Selected Methodologies Convenient for the Synthesis of *N*,5-Diaryloxazole-2-amine Pharmacophore

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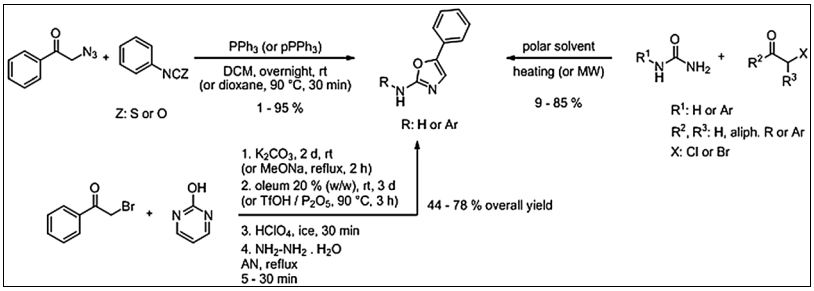

N,5-Diaryloxazole-2-amine moiety is a strong pharmacophore found in 775 biologically active compounds possessing antitumor, anti-infective, immunosuppressive, anti-inflammatory, and other activities. Despite a broad biological exploitation, synthesis of *N*,5-diaryloxazole-2-amine-containing compounds is still not well developed. Preparation of oxazole-2-amine moiety is a relatively complex topic, and often low yields are observed. In this article, we discussed four synthetic methodologies and provided some generalization of their advantages, as well as further synthetic development. Using these methodologies, we prepared all together 10 new oxazole-2-amine derivatives and discovered presence of urea and enamine side products.

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INTRODUCTION

Databases Reaxys and SciFinder Scholar describe 775 *N*,5-diaryloxazole-2-amine-containing compounds possessing biological activity [1,2]. *N*,5-Diphenyloxazole-2-amine (**1**) represents a pharmacophoric fragment that can be found in many biologically active compounds (e.g., Fig. 1). Compounds containing *N*,5-diaryloxazole-2-amine moiety are mostly antineoplastic species targeting the following: VEGF receptors (264 molecules) [3], inosine monophosphate dehydrogenase II (242) [4], epidermal growth factor receptors (228) [5], cyclin-dependent kinases 2 and 4 (225) [5], platelet-derived growth factor receptors (225) [5], capsaicin receptors (87) [6], protein tyrosine phosphatase 1B (55) [7], blood-coagulation factor VIIa (50) [8], diacylglycerol acyltransferase (41) [9], cKit tyrosine kinase (19) [10], Flt1 and Flt3 receptor kinases (18) [11], BCR-ABL kinase (18) [9], tubulins (16) [12], and fibroblast growth factor receptors (7) [13]. Derivatives of *N*,5-diaryloxazole-2-amine **1** are described as anti-angiogenic and antitumor agents [3,4], antibiotics [8], immunosuppressants [8], anti-inflammatory compounds [8], antiviral compounds [4], fungicides [4], platelet aggregation inhibitors [4], antirheumatics [10], antidiabetics [7], anti-obesity agents [8], anti-arteriosclerotics [10], and allergy inhibitors [9].

Selected methods for preparation of *N*,5-diaryloxazole-2-amines. The distinguished biological importance of *N*, 5-diaryloxazole-2-amine-containing compounds inspired us to prepare a set of novel VEGFR-2 inhibitors on the basis of the structure of **AAZ** inhibitor (PDB complex: 1Y6A, Fig. 1). *N*,5-Diphenyloxazol-2-amine (**1**) was discovered to have inhibition activity against the VEGFR2 tyrosine kinase ($IC_{50} = 1.2\ \mu M$) [5]. Further investigation of this structure leads to preparation of two highly active inhibitors – **AAZ** and **AAX** (Fig. 1) [3]. This study also introduced into the structure new pharmacophoric groups – the SO_2R and MeO groups on one aromatic ring and the pyridyl ring in the meta position of the other phenyl ring. With the help of *in silico* methods, we designed a number of novel compounds with additional pharmacophoric groups [13]. Convenient synthesis of oxazole-2-amines is an important part in the development of these inhibitors. For this purpose, we used a number of synthetic methods for their preparation. In this section, we present some details known about the four main methods and some observations we made on the basis of available data.

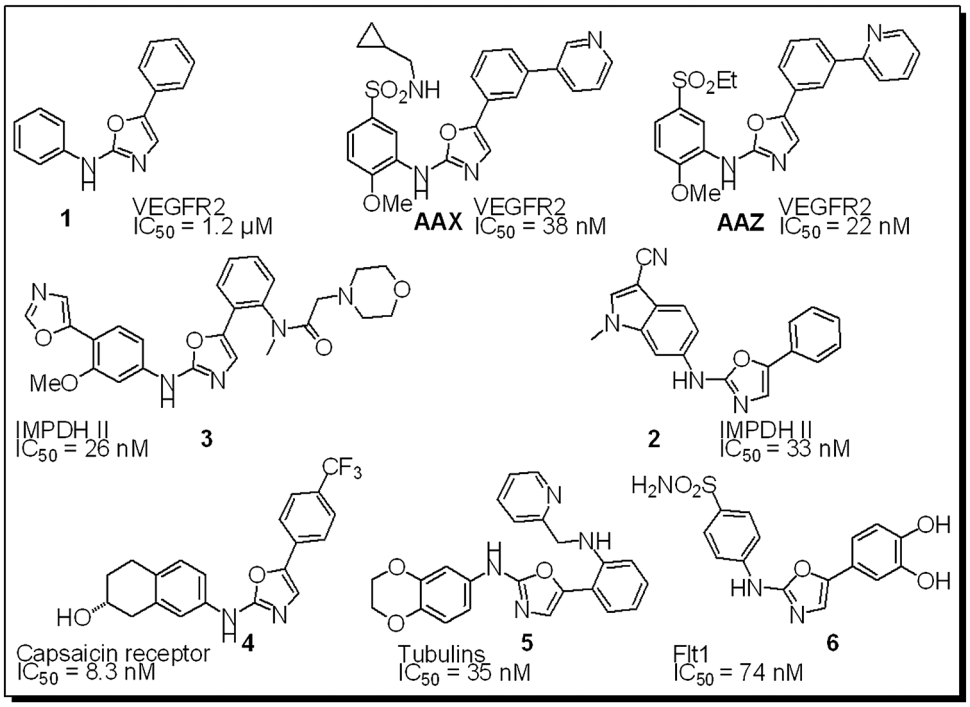
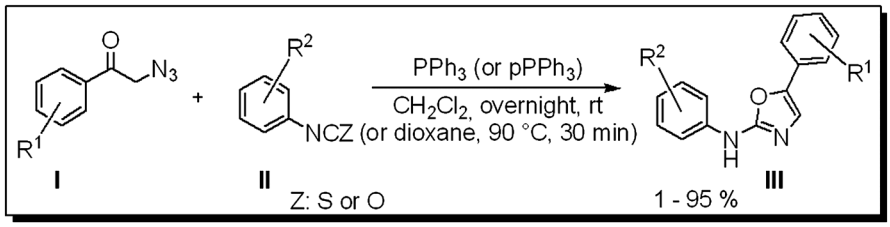


Figure 1. Structure of *N*,5-diphenyloxazole-2-amine (**1**) and some examples of other powerful bioactive compounds possessing this fragment (in bold) depicted with their activity on particular biological target; for example, inhibitors of VEGFR2: **AAX** and **AAZ** from PDB complexes: 1Y6B and 1Y6A [3], respectively, inosine monophosphate dehydrogenase II inhibitors **2** and **3** [4], Capsaicin receptor **4** [6], tubulins **5** [12], and Flt1 kinase inhibitor **6** [11].

Scheme 1. Reaction conditions exploited for the synthesis of *N*,5-diaryloxazole-2-amines **III**. R^1 and R^2 substituents are depicted in Table 1.



1. "The azaylide methodology": the reaction of α-azidoketones I with isocyanates (or isothiocyanates) II. The synthesis of the required *N*,5-diaryloxazole-2-amines **III** was described in the literature by the reaction of α-azidoacetophenones **I** with arylisothiocyanates **II** (Z: S) [3] (Scheme 1). These reactions required PPh_3 (or $pPPh_3$, a resin-bound triphenylphosphine) and were currently described at two conditions: (A) overnight stirring at room temperature in CH_2Cl_2 [3] or (B) 30-min heating at 90 °C in dioxane [14]. The yields of oxazoles **III** obtained by this methodology are described in the literature in a very broad range (1–95%) [3,6,15]. The yields seem to be dependent on the structure of substrates **I** and **II** (Table 1).

The relationship between the structure of the starting materials **I** and **II** and the obtained yields for the oxazole compound **III** according our knowledge was never generalized before. Even though the literature sources are limited, some conclusions can be made. The entries 1–10 (reaction conditions A) in Table 1 represent the effect of various functional groups and their positions on the aromatic ring of the α-azidoacetophenones **I** that react with the same 2-isothiocyanato-1-methoxy-4-(methylsulfonyl) benzene (**II**). In these cases, the best yields were obtained with electron-donating substituents (R^1: MeO) in meta or para positions at α-azidoacetophenones **I** (Table 1, entries 7 and 8, 49–58%), whereas MeO group in para position seems to be more favorable (entry 8, 58%). On the other side, the lowest yields were achieved with electron-withdrawing groups: (R^1: CN) in both meta and para positions (Table 1, entries 9 and 10, 1–6%). Halogen-substituted α-azidoketones **I** gave the yields mostly between the aforementioned values (Table 1, entries 1–6) [3]. Similar trends can be seen in entries 11–13 (Table 1): azidoketone **I**

Table 1

Observed yields of the oxazoles **III** in dependence on the structure of the starting α-azidoketones **I** and the arylisothiocyanates (**II**, Z: S).

	R^1 from **I**	R^2 from **II**	Reaction condition	**III** (%)
1	2-Cl	5-SO_2Et, 2-OMe	12PPh_3, A	25
2	3-Cl	5-SO_2Et, 2-OMe	PPh_3, A	3
3	4-Cl	5-SO_2Et, 2-OMe	PPh_3, A	10
4	3-F	5-SO_2Et, 2-OMe	PPh_3, A	27
5	4-F	5-SO_2Et, 2-OMe	PPh_3, A	19
6	3-Br	5-SO_2Et, 2-OMe	PPh_3, A	36
7	3-MeO	5-SO_2Et, 2-OMe	PPh_3, A	49
8	4-MeO	5-SO_2Et, 2-OMe	PPh_3, A	58
9	3-CN	5-SO_2Et, 2-OMe	PPh_3, A	1
10	4-CN	5-SO_2Et, 2-OMe	PPh_3, A	6
11	2-N(Me) $COCH_2OAc$	3-MeO, 4-(oxazol-4-yl)	pPPh_3, B	95
12	2-NO_2	3-MeO, 4-(oxazol-4-yl)	pPPh_3, B	70
13	2-COOEt	3-MeO, 4-(oxazol-4-yl)	pPPh_3, B	50
14	H	3-MeO, 4-CN	pPPh_3, B	67
15	H	3-MeO, 4-COOEt	pPPh_3, B	69
16	H	3-CF_3, 4-CN	pPPh_3, B	50

Reaction conditions A: CH_2Cl_2, rt, overnight; B: dioxane, 90 °C, 30 min.

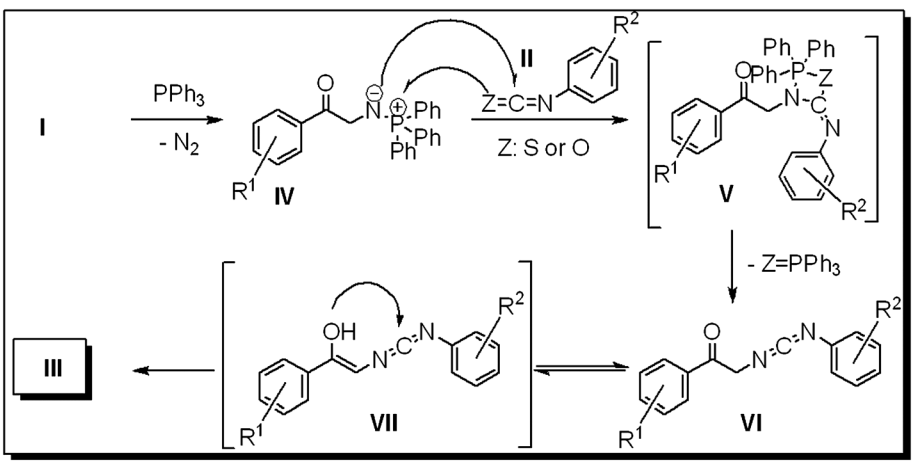
with electron-donating substituent reacts with better yield [6]. However, in these cases, the substituents are in ortho position, which might bear also other effects (e.g., steric and H-bond).

Positive effect of the MeO group on arylisothiocyanates **II** can be seen also in entries 14–16 (Table 1) [15]. Even though generalization is this case is more or less speculative because few examples are available. Also important seems to be that the reaction conditions B (dioxane at 90 °C within 30 min) provide higher yields. Even though different reaction conditions have been used, it seems that the structure of arylisothiocyanates **II** have weaker impact on the yields of **III** compared with **I** (see Table 1, entries 14–16, describing quite similar yields for different substitution only on **II** and entries 1–10 that have very different yields with different substitution only on **I**).

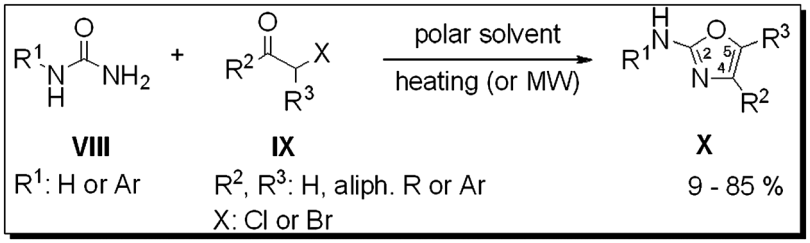
In the proposed mechanism of oxazol formation, PPh_3 reacts with α-azidoacetophenone **I** to form organic azaylide **IV** analogically to the Staudinger reaction [16]. The formed azaylide **IV** attacks organic isothiocyanate (or isocyanate) **II** and performs carbodiimide **VI** [17]. However, the effect of electron-donating/withdrawing properties of aryl substituent(s) in α-azidoacetophenones **I** on the rate of intramolecular oxazole ring formation is probably based on the ability to form the enol intermediate **VII**, which leads to an oxazolic ring in **III** (Scheme 2).

2. "The urea methodology": a reaction of urea (7) or its derivatives VIII with α-halocarbonyls IX. The reaction of urea (**7**) or its derivatives **VIII** with α-bromo (or α-chloro) ketones or aldehydes **IX** represents a useful methodology for the synthesis of oxazole-2-amines **X** (Scheme 3) [18]. Syntheses of oxazole-2-amines **X** from urea (**7**) [19,20] or

Scheme 2. A mechanism of "the azaylide methodology" describing the reaction of α-azidoacetophenones **I** with isothiocyanates (or isocyanates) **II** in the presence of PPh_3.



Scheme 3. Synthesis of substituted oxazolamines **X** performed from ureas **VIII** and α-halocarbonyls **IX**.



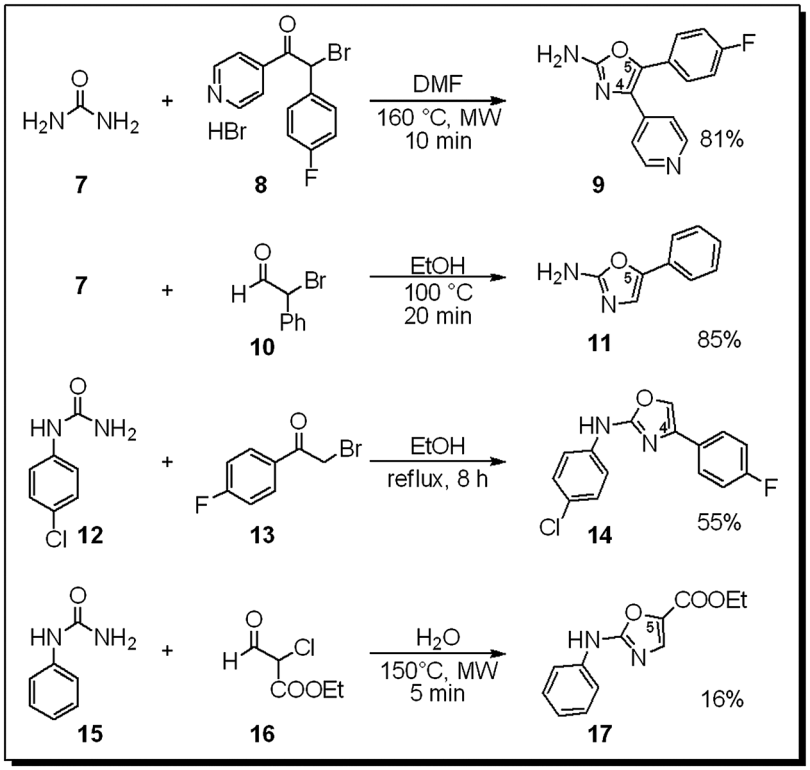
urea derivatives **VIII** [21–23] with α-halocarbonyls **IX** are described from low to good yields (9–85%). The synthesis of oxazoles **X** by this methodology was carried out in various polar solvents (water [24], ethanol [25], alcohols [26], acetonitrile, acetic acid, dioxane, or DMF) by heating or by microwave irradiation [22,27] (Scheme 3).

By this method, a number of oxazolic products **X** were obtained in good yields (examples in Scheme 4). This synthetic methodology seems to be quite flexible because the structure of the product **X** obtained by this method depends on the character and substitution of the starting compounds. When **IX** is an α-haloketone, *N*,4-diaryloxazole-2-amine **14** (a regioisomer to the *N*,5-diaryloxazole-2-amine **III**) or 4,5-diaryloxazole-2-amine **9** is formed. In case **IX** is an α-haloaldehyde, 5-aryloxazole-2-amine **11** can be obtained in good 85% yield [23], and also *N*-aryloxazole-2-amine, for example, **17**, can be formed [20] (Scheme 4). Although no *N*,5-diaryloxazole-2-amines **III** were prepared, yet by this methodology, its precursor 5-aryloxazole-2-amine **11** was obtained in high 85% yield. 5-Aryloxazole-2-amines such as **11** can be effectively transformed to the required *N*,5-diaryloxazole-2-amine **III** by "the 2-chlorooxazole methodology" as we will show later.

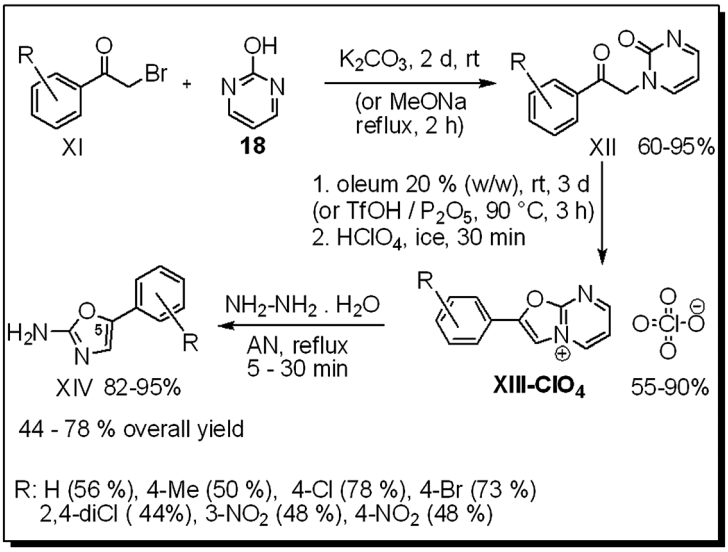
3. "The 2-hydroxypyrimidine methodology": the reaction of α-bromoacetophenones XI with 2-hydroxypyrimidine 18. A quite unusual and convenient approach for the preparation of 5-aryloxazole-2-amines **XIV** was published recently [28]. It represents a three-step synthesis starting from α-bromoacetophenones **XI** and 2-hydroxypyrimidine hydrochloride (**18**) (Scheme 5).

In the first step, one of the pyrimidine nitrogens undergoes alkylation with α-bromoacetophenones **XI** in the presence of K_2CO_3 (or MeONa in cases when R: 2, 4-diCl, 3-NO_2, and 4-NO_2). Afterward, a protonation of

Scheme 4. Reactions performed from urea (**7**) or urea derivatives **12** and **15** and α-halocarbonyls.



Scheme 5. Preparation of 5-aryloxazole-2-amines **XIV** from α-bromoacetophenones **XI** and 2-hydroxypyrimidine (**18**).



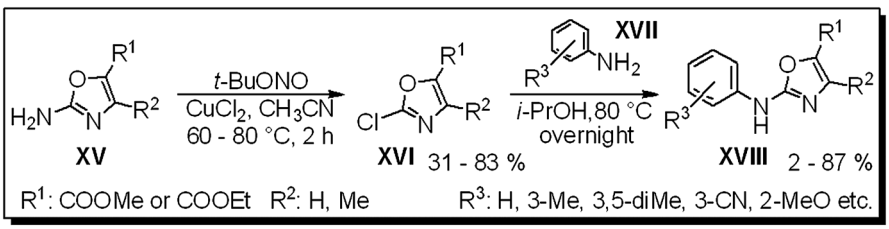
an intermediate **XII** by a super acid (either oleum: 20% (w/w) SO_3 in conc. H_2SO_4 or alternatively by a mixture of TfOH/P_2O_5) causes carbonyl group enolization and subsequent oxazole ring formation to give 2-aryloxazolo [3,2-*a*]pyrimidin-4-ium sulfate **XIII-SO$_4$**. This salt is transferred by conc. $HClO_4$ to the less soluble perchlorate **XIII-ClO$_4$** that precipitates from the solution. "The 2-hydroxypyrimidine methodology" is performing well with electron-deficient aromatic ring of acetophenone **XI**. When substituent(s) on the aromatic ring of **XI** are electron donating, the present oleum can sulfonate the electron-rich aromatic ring on **XI**. In such cases, instead of oleum, a mixture of TfOH/P_2O_5 was employed (e.g., **XI**, R: H or Me). Despite the aforementioned alternative in the reaction conditions, acetophenone derivative **XI** (R: 4-MeO) performed only decomposition products [28]. In the last reaction step, hydrazine opens the annulated pyrimidine ring in **XIII-ClO4**, which leads to 5-aryloxazole-2-amines **XIV** in 44–78% overall yield [28] (Scheme 5).

4. "The 2-chlorooxazol methodology": the preparation of N-aryloxazole-2-amines XVIII from 2-chlorooxazoles XVI. *N*-Aryloxazole-2-amines **XVIII** can be prepared in two steps starting from 2-aminooxazol-5-carboxylates **XV** [29] and derivatives of anilines **XVII** [3,6] (Scheme 6). Compounds **XV** were transformed to 2-chlorooxazoles **XVI** in 31–83% yields by *t*-BuONO/$CuCl_2$ [30,31]. Reaction of anilines **XVII** with 2-chlorooxazoles **XVI** was described to give *N*-aryloxazole-2-amines **XVIII** in 2–87% yield in *i*-PrOH (*i*-BuOH or acetonitrile) at 80 °C [6]. 5-Aryloxazole-2-amines obtained for instance by the previous "urea methodology" (Scheme 4, 9, or 11) or "2-hydroxypyrimidine methodology" (Scheme 5, **XIV**) are useful precursors for the synthesis of the required *N*,5-diaryloxazole-2-amines **III**. A combination of these approaches is a significant tool for the preparation of the required *N*,5-diaryloxazole-2-amines **III**.

RESULTS AND DISCUSSION

1. "The azaylide methodology": performed reactions between α-azidoketones XIX and isocyanate 19. Following "the azaylide methodology," we performed 10 experiments in order to prepare the desired *N*-aryloxazoles **XX** (Scheme 7, Table 2). Some of the performed experiments were carried out in dioxane at 90 °C within 30 min (Table 2, entries 2 and 6–8). In two cases, the reaction was performed at both reaction conditions, and reactions at higher

Scheme 6. Synthesis of *N*-aryloxazole-2-amines **XVIII** from oxazole-2-amines **XV**.



Scheme 7. Synthesis of *N*-aryl-2-aminooxazoles **XX** and their urea byproducts **XXI** from different α-azidoketones **XIX** and 2-isocyanato-1-methoxy-4-(methylsulfonyl)benzene (**19**) (R substituents are depicted in the Table 2).

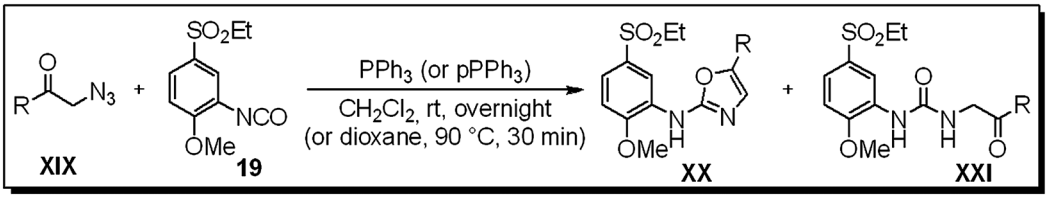


Table 2

The result of reactions between different α-azidoketones **XIX** with isocyanate **19**.

	XIX	R	Reaction condition	XX (%)[b]	XXI (%)[b]
1	**a**	3-BrPh	PPh_3, A	28	0
2	**a**	3-BrPh	$pPPh_3$,[a] B	**35**	0
3	**b**	3,5-diBrPh	$pPPh_3$,[a] A	19	26
4	**c**	3-Br,5-MeOPh	$pPPh_3$,[a] A	0	10
5	**d**	3-Br,4-MOMOPh[c]	$pPPh_3$,[a] A	31	29
6	**d**	3-Br,4-MOMOPh[c]	$pPPh_3$,[a] B	**40**	15
7	**e**	3-Br,5-BnOPh	$pPPh_3$,[a] B	0	0
8	**f**	3-Br,5-NO_2Ph	$pPPh_3$,[a] B	0	0
9	**g**	Me	PPh_3, A	27	0
10	**h**	CH_2COOEt	PPh_3, A	25	0

The reaction conditions and the yields of *N*-aryloxazole-2-amines **XX** and urea-containing byproducts **XXI** are depicted. Reaction conditions A: CH_2Cl_2, rt, overnight; B: dioxane, 90 °C, 30 min.
[a]$pPPh_3$ is a resin bound triphenylphosphine (a commercial copolymer containing an equivalent of 1.6 mmol/g of PPh_3).
[b]Obtained after FLC purification.
[c]MOM, methoxymethyl group.

temperature resulted in better yields for *N*-aryloxazole-2-amines **XX** (Table 2, entries 1 and 2 and 5 and 6).

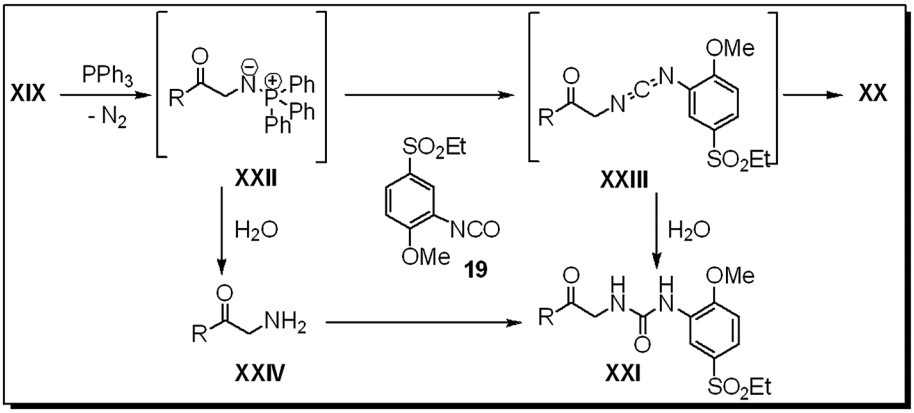
Within our study, novel urea-containing byproducts **XXI** were identified. The reactions between α-azidoketones **XIX** (**XIXb–d**) and isocyanate **19** favored the formation of byproducts **XXI** (Table 2, entries 3–5). Within this methodology, the urea products **XXI** were not yet reported in the literature. The presence of highly polar and therefore easily by TLC (or flash liquid chromatography (FLC)) overlooked urea byproducts **XXI** can partially explain low yields obtained for *N*,5-diaryloxazole-2-amines **III** in the literature. (Table 1, entries 1–10, 1–58%). Reaction condition B (dioxane, 90 °C, 30 min) not only gave a higher yield of the desired *N*-aryloxazole-2-amines **XX** but also favored **XX** over the urea byproducts **XXI** (Table 2, entries 5 and 6). In some of our experiments starting from **XIXa** (or **XIXg** or **XIXh**), solely oxazole product **XX** without any urea side product **XXI** was obtained (Table 2, entries 1 and 2 and 9 and 10).

The urea derivatives **XXI** could be formed either by Staudinger reaction that transforms azidoketones **XIX** in the presence of PPh_3 or by traces of water to α-aminoketones **XXIV** that can further react with isocyanate **19** to give polar urea side products **XXI**. Alternatively, the urea compounds **XXI** could be formed from carbodiimide intermediates **XXIII** and water or more probably from not transformed **XXIII** during separation of the crude reaction mixture by FLC on silica (Scheme 8).

The results described in the literature and obtained from our experiments with the same starting α-azidoacetophenone **XIXa** (3-BrPh) were comparable. The compound **XIXa** performed either with arylisothiocyanate **II** (5-SO_2Et,-2-OMe) at rt in 36% (Table 1, entry 8) or with arylisocyanate **19** (5-SO_2Et,-2-OMe) at rt (or at 90 °C) in 28% (or 35%) yield (Table 2, entry 1 or 2). No urea side product **XXI** was seen in these experiments. This observation can support the possibility that in the case when **XXIII** is reactive enough, only the oxazole **XX** can be formed (Scheme 8).

In the previous text (the study of data from literature), we have concluded that the electron-donating substituent (3-MeO or 4-MeO) on the aromatic ring of α-azidoacetophenones **I** is advantageous and gives the best yield of *N*,5-diaryloxazole-2-amines **III** (Table 1, entries 6 and 7, 49–58%). In most of our performed reactions, we used an azidoketone **XIX** with two different substituents, and we expected an effect from both, as well as from their positions on the aromatic ring. We have observed a dependence on substituent similar as in literature in our reactions performed with α-azidoketone **XIXd** (3-Br,4-MOMO) and isocyanate **19** by both rt and 90 °C (Table 2, entries 5 and 6, 31–40%). If the electron-donating substituent was on the meta position, for example,

Scheme 8. Proposed mechanism yielding *N*-aryloxazole-2-amines **XX** and the urea side products **XXI**.



XIXc (3-Br,5-MeOPh) or **XIXe** (3-Br,5-BnOPh), the oxazole product **XX** was not formed even though the last reaction was performed in dioxane at 90 °C (Table 2, entry 4 or 7). This shows that the positive effect of electron-donating substituents in meta position is way lower, especially in combination with a bromine substituent in the other meta position. Further studies for a broader library of starting materials for this methodology are required in order to discover what other substituents give a yield-wise positive response.

The "azaylid methodology" is quick; the starting material can be prepared easily and has potential to provide an oxazole-2-amine products. However, its dependence on the structure of starting compounds brings unreliability into the synthesis, and the yields can be very different from case to case. Especially substituents in meta position and/or electron-withdrawing groups on aromatic ring of the ketoazide **XIX** may lower the overall yield, as we have proven. We have shown that this method can be also used on aliphatic ketoazides (**XIXg**,**h**).

2. "The urea methodology": reactions between urea (7) and *N*-arylurea 21 with α-halocarbonyls 16 or 22. A reaction between the urea (**7**) and aliphatic ethyl 2-chloro-3-oxopropanoate (**16**) in water at 100 °C within 1.5 h performed ethyl oxazole-2-aminocarboxylate (**20**) in 64% yield (Scheme 9). This reaction was not yet described, and it is complementary to the only exceptionally occurred reactions of acyclic α-haloaldehydes (**10** or **16**) with urea derivatives known from literature (Scheme 4) that shows exploitation of "the urea methodology" for the synthesis of 5-aryl and *N*-aryloxazole-2-amines **11** and **17**.

We performed also the reaction between 5-(ethylsulfonyl)-2-methoxyfenylurea (**21**) and 2-bromo-1-(3-bromophenyl)ethanone (**22**) in refluxing ethanol within 24 h. The reaction gave 4-aryloxazole-2-amine **23** in 47% yield (Scheme 9). Its required regioisomeric 5-aryloxazole-2-amine product was prepared in 36% yield by "the azaylid methodology" from α-azidoacetophenone **I** and isothiocyanate **II** (Table 1, entry 8).

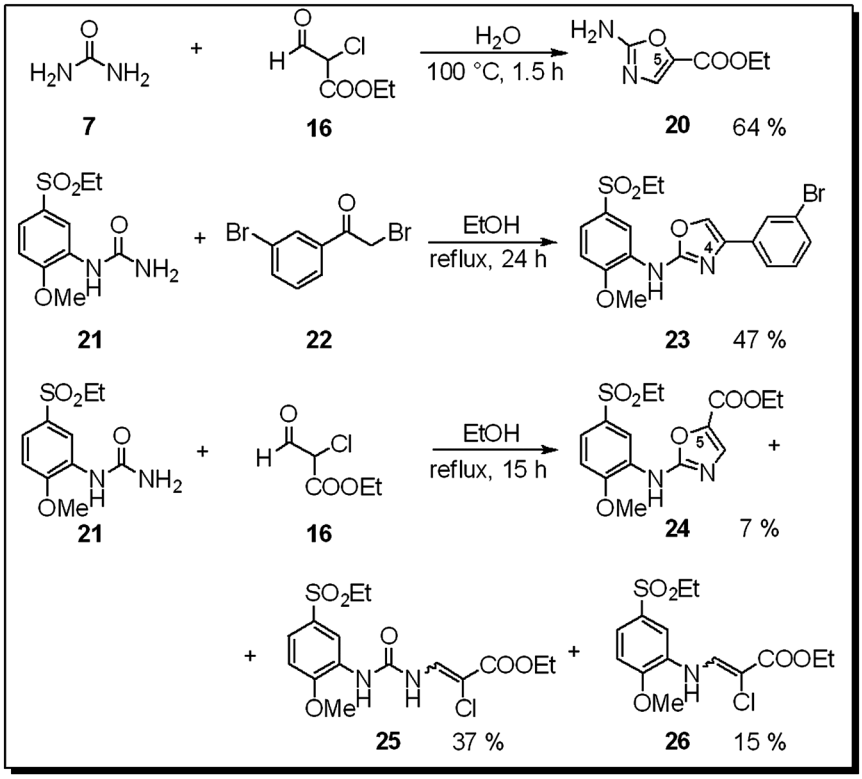
The reaction of *N*-arylurea **21** with acyclic ethyl 2-chloro-3-oxopropionate (**16**) was not yet described. The low 7% yield of the *N*-aryloxazole-2-amine product **24** was accompanied by undesired side products **25** (37%) and **26** (15%). The last one resulted from ethyl 2-chloro-3-oxopropionate (**16**) and 5-(ethylsulfonyl)-2-methoxyaniline formed *in situ* by decomposition of **21** in EtOH within the reaction conditions.

The "urea methodology" has potential to prepare a wide range of oxazol-2-amine derivatives – especially *N*,4-di-substituted derivatives in good yield and oxazole-2-amines with primary amino group. The highest benefit of this method is providing of substrates (compound **20**) for the "2-chlorooxazole methodology", which is discussed later.

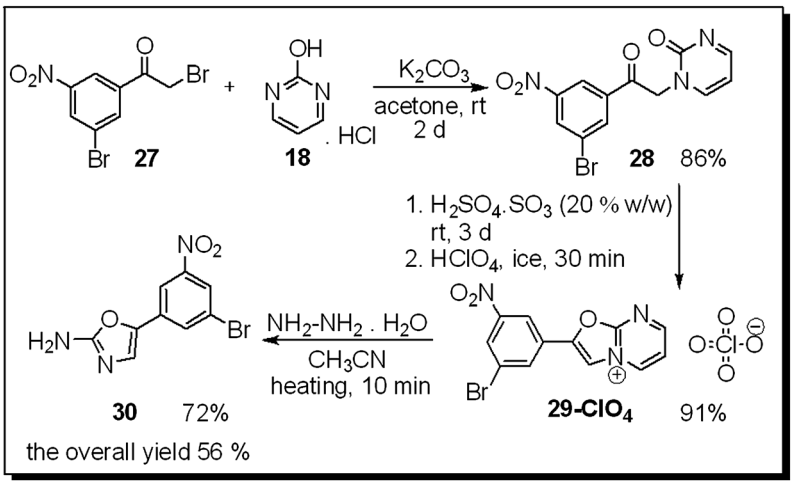
3. "The 2-hydroxypyrimidine methodology": a synthesis of 5-aryloxazole-2-amine 30. As we have shown in the Introduction section, "the 2-hydroxypyrimidine methodology" can be exploited successfully for the synthesis of electron-deficient 5-aryloxazole-2-amines **XIV** (Scheme 5). Because this method is relatively new, we decided to use it to prepare 5-(3-bromo-5-nitrophenyl)oxazole-2-amine (**30**) – a compound with highly electron-withdrawing nitro group on aromatic ring of starting bromoketone **27** (Scheme 10). The *N*-alkylated pyrimidin-2-one **28** was prepared from α-bromoacetophenone **27** and 2-hydroxypyrimidine hydrochloride (**18**) at rt within 2 days in 86% yield. The sulfate salt of **29** was formed from **28** by 20% (w/w) oleum at rt within 3 days. Subsequent work-up with perchloric acid and short reaction with hydrazine hydrate (10 min) provided the 5-aryloxazole-2-amine **30** in a good overall 56% yield (three steps) (Scheme 10). When hydrazine was allowed to react with **29-ClO$_4$** for a longer reaction time (45 min), we observed a reduction of nitro to amino group in oxazole **30**.

We also wanted to test the limitation of this method, so we applied the same reaction conditions as that mentioned earlier on 1-(3-(benzyloxy)-5-bromophenyl)-2-bromoethanone (R: 3-BnO,5-Br). In this case, in accordance with literature expectations [28], oleum sulfonated the

Scheme 9. Reactions between ureas (**7** or **21**) and α-haloketones (**16** or **22**).



Scheme 10. A three-step synthesis of 5-aryloxazole-2-amine **30** from α-bromoketone **27** and 2-hydroxypyrimidin hydrochloride (**18**).

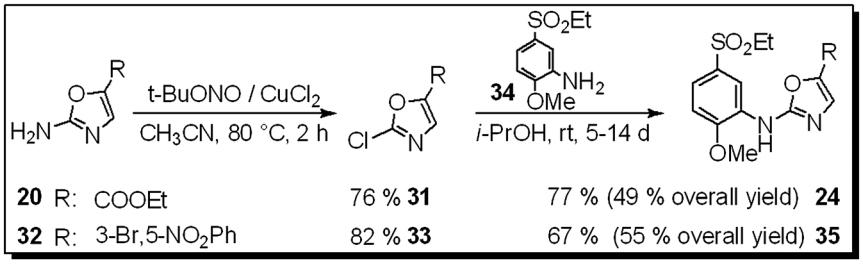


electron-rich aromatic ring bearing BnO group. A failure was observed also by the alternative reaction conditions using $TfOH/P_2O_5$, which were recommended by literature [28] in cases of electron-rich starting acetophenones **XI** (Scheme 5 and therein).

Even though the "2-hydroxypyrimidine methodology" requires three synthetic steps, it is undoubtedly useful for the preparation of oxazol-2-amines with electron-withdrawing or halogen-substituted bromoketones with good yields. This method should be avoided though for substrates with electron-donating substituents. Also, this method provides substrates for the "2-chlorooxazole methodology."

4. "The 2-chlorooxazol methodology": reactions between 2-chlorooxazoles 31 or 33 and aniline 34. To prepare *N*-aryloxazole-2-amines **24** (or **35**) starting from oxazole-2-amines **20** (or **32**), we used "the 2-chlorooxazol

Scheme 11. Synthesis of *N*-aryloxazole-2-amine **24** (or **35**) via "the 2-chlorooxazole methodology" starting from the oxazole-2-amine **31** (or **33**).



methodology" introduced in Scheme 6 and therein. The substitution of amino to chloro group via the reaction of **20** (or **32**) with *t*-BuONO/$CuCl_2$ in CH_3CN performed 2-chlorooxazoles **31** (or **33**). When intermediate **31** was heated with aniline derivative **34** in *i*-PrOH, according to the conditions described in the literature [30], only products of decomposition were observed. Therefore, we developed modification of the reaction of 2-chlorooxazol derivatives **31** (or **33**) with aniline **34** at much milder conditions (*i*-PrOH, rt, 5–14 days, portion wise addition of an excess of 2-chlorooxazol derivative within a long reaction time). The course of reaction was monitored by consumption of the starting aniline **34** on TLC. By this low temperature modification, novel *N*-aryloxazole-2-amine products **24** (or **35**) were obtained in 77 (or 67%) yield (Scheme 11) in a more reliable manner.

The "2-chlorooxazole methodology" represents a versatile method for the synthesis of *N*,5-diaryloxazole-2-amines – derivatives of **III** (Fig. 1). The synthesis of **35** made exploitation of many 5-aryloxazole-2-amine intermediates prepared by the "urea" or "2-hydroxypyrimidine" methodologies (e.g., Scheme 4, compounds **9** or **11** or Scheme 5, products **XIV**) possible. Heating in the second synthetic step should be avoided to minimize decomposition of 2-chlorooxazole intermediate, which on the other side lengthens reaction times.

CONCLUSION

In this article, we compared four methodologies that can be alone or in combination used for the synthesis of the oxazole-2-amine pharmacophore. "The azaylide methodology" proved to be useful in cases the azide **XIX** bears an electron-donating substituent in para position (e.g., 4-OMOM, compound **XIXd**, Table 2). However, meta and/or electron-withdrawing substituents of azides **XIX** provide very low yields, especially double meta-substituted azides **XIX** (Table 2). Therefore, this method should be avoided in these cases. Within our experiments, we discovered novel urea-fragment-containing byproducts **XXI** (Scheme 7, Table 2). The mechanism explaining the formation of **XXI** was proposed (Scheme 8). We were able to prepare a number of novel VEGFR2 inhibitors using this method (e.g., 3 bispyridyl, *para*-OH and *para*-OMe derivatives of **AAZ**) [32].

"The urea methodology" represents a general synthetic way to prepare variously substituted oxazol-2-amines mostly in moderate to good yields (Scheme 3). This method is useful to prepare *N*,4-diaryloxazol-2-amines **X** (Scheme 9, compound **23**, 47%). Even though a direct preparation of *N*-aryloxazole-2-amine **24** by this method was a setback (yield of oxazole product only 7% at best and presence of two novel enamine products **25** and **26**), this method was used for the preparation of the precursor ethyl 2-aminooxazole-5-carboxylate (**20**), which can be used further in the "2-chlorooxazol methodology" (Scheme 11, compound **24**).

"The 2-hydroxypyridine methodology" represents a convenient substitute method to the "azaylide methodology," for it can be used for the synthesis of electron-deficient 5-aryloxazol-2-amines (e.g., compound **30**, Scheme 10, 3-Br,5-NO_2 substitution). However, a synthesis of electron-rich 5-aryloxazol-2-amines by this method is limited because undesired sulfonation of activated aromatic ring (with oleum) or decomposition processes (with TfOH/P_2O_5) used to occur within the reaction conditions.

"The 2-chlorooxazol methodology" is a useful tool for the transformation of 5-aryloxazole-2-amine precursors (obtained by the "urea methodology" or by the "2-hydroxypyridine methodology") to *N*-arylamineoxazoles (e.g., **24** and **35**, Scheme 11). We discovered that using of heating in the second step (80 °C, *i*-PrOH, overnight) provided only products of decomposition. To ensure the formation of oxazoles **24** and **35** in good yields, we successfully refined the reaction conditions (rt, *i*-PrOH, 5–14 days;). The oxazole **35** is an important intermediate for further preparation of new VEGFR2 inhibitors (*meta-N* and *meta-O* substituted derivatives of **AAZ**) [32].

EXPERIMENTAL

Materials and methods. ^1H and ^{13}C NMR spectra were recorded on Varian Gemini (300 and 75 MHz, respectively), chemical shifts are in ppm, and TMS was used as an internal

standard and $CDCl_3$ or DMSO-d_6 as the solvent. IR spectra were acquired on FT-IR-ATR REACT IR 1000 (ASI Applied Systems) with diamond probe and MTS detector. Mass spectra were performed on LC/MS (Agilent Technologies 1200 Series equipped with Mass spectrometer Agilent Technologies 6100 Quadrupole LC/MS) and GC/MS (Agilent Technologies 6890N gas chromatograph with a 5973 Network mass-selective detector (Agilent, Waldbronn, Germany). The course of the reactions was followed by TLC analysis (Merck silica gel 60 F_{254}). UV lamp (254 nm) and iodine vapors were used for the visualization of TLC spots. Melting points were measured using Kofler apparatus or Barnstead Electrothermal IA9200 and are uncorrected. Starting material and reagents were bought from Sigma-Aldrich, Fluka (Local Office, Bratislava, Slovakia), or Acros (Geel, Belgium). Some of the starting compounds (isocyanate **19** and arylurea **21**) for the preparation of oxazole-2-amine had to be prepared.

4-(Ethylsulfonyl)-2-isocyanato-1-methoxybenzene (19). Recently, we have described the synthesis of 5-(ethylsulfonyl)-2-methoxyaniline (**19a**) from commercial 4-methoxybenzenesulfonyl chloride (or anisol) [33]. 4-(Ethylsulfonyl)-2-isocyanato-1-methoxybenzene (**19**) was prepared by heating of 500.0 mg of aniline 5-(ethylsulfonyl)-2-methoxyaniline (**19a**) (2.30 mmol, 1.00 mol eq) in 10 mL of toluene (abs.) with4.0 mL (5.25 mmol, 3.20 mol eq, 20% w/w in toluene) phosgene solution to reflux within 3 h. Subsequently, the reaction mixture was worked up by rotary vacuum evaporation (RVE). The product was obtained as 504 mg (2.25 mmol, 97.8%) of brown solid. mp 101.8–104.3 °C. IR ν (solid): 3017 (w), 2868 (m), 2264 (w), 1603 (s), 1451 (m), 1308 (s, S=O), 1260 (s), 1123 (s, S=O), 1044 (s), 737 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.27 (t, 3H, J = 7.4 Hz, $SO_2CH_2CH_3$), 3.08 (q, 2H, J = 7.4 Hz, SO_2CH_2), 4.04 (s, 3H, OCH_3), 7.02 (d, 1H, J(3,4) = 8.7 Hz, C_3–H), 7.52 (d, 1H, J (4,6) = 2.3 Hz, C_6–H), 7.72 (dd, 1H, J(3,4) = 8.7 Hz, J(4,6) = 2.3 Hz, C_4–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.3 ($SO_2CH_2CH_3$), 49.6 (SO_2CH_2), 56.3 (OCH_3), 110.8 (C_3), 117.3 (C_6), 122.5 (C_4), 129.0 (C_1), 130.0 (C_5), 151.5 (C_2), 152.3 (N=*C*=O). *Anal.* Calcd for $C_{10}H_{11}NO_4S$ (241.26): C, 49.78; H, 4.60; N, 5.81; S, 13.29. Found: C, 49.82; H, 4.65; N, 5.75; S, 13.24.

General procedure for "the azaylide reaction" (XX, XXI). Method A: To a solution of 262.0 mg (1.00 mmol, 1.00 mol eq) of PPh_3 in 2 mL of dry CH_2Cl_2 [or a suspension of 624.0 mg (1.00 mmol, 1.00 mol eq) of pPPh_3 (1.6 mmol/g of polystyrene bound PPh_3) in 4.5 mL of dry CH_2Cl_2], a solution of α-azidoacetophenone **XIXa–h** (1.00 mmol, 1.00 mol eq) and 288.0 mg (1.20 mmol, 1.20 mol eq) of 5-(ethylsulfonyl)-2-methoxyphenylisocyanate (**21**) in 4.5 mL of CH_2Cl_2 (abs) was added dropwise at 0 °C within 2 h. Afterward, the reaction mixture was stirred at rt overnight.

Method B: To a suspension of 624.0 mg (1.00 mmol, 1.00 mol eq) of pPPh_3 (1.6 mmol/g, polystyrene bound PPh_3) in 7.5 ml of dioxane abs, a solution of α-azidoacetophenone **XIXa–h** (1.00 mmol, 1.00 mol eq) and 288.0 mg (1.20 mmol, 1.20 mol eq) of 5-(ethylsulfonyl) -2-methoxyphenylisocyanate (**19**) was added at once at rt. The mixture was heated at 90 °C for 30 min, cooled to rt, filtered off to remove the resin, and the solvent evaporated on RVE. The oxazole product **XXa–f** and urea derivatives **XXIb–d** were isolated by FLC on silica gel (EA/Hex = 1 : 1 or 2 : 1).

5-(3-Bromophenyl)-N-[5-(ethylsulfonyl)-2-methoxyphenyl] oxazole-2-amine (XXa). This compound was obtained by method A 122.0 mg (0.28 mmol, 28.0%) and by method B 153.0 mg (0.35 mmol, 35.0%) as a white powder. mp 182.0–183.0 °C [EA/Hex] [3]. IR ν (solid): 3386 (m, NH), 2998 (w), 1569 (s), 1543 (m), 1514 (m), 1404 (m), 1312 (s, S=O), 1260 (s), 1125 (s, S=O), 1021 (s), 748 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, J = 7.3 Hz, CH_2CH_3), 3.18 (q, 2H, J = 7.3 Hz, CH_2CH_3), 4.04 (s, 3H, OCH_3), 7.02 (d, 1H, J(3,4) = 8.6 Hz, C_3–H), 7.21 (s, 1H, C_{4*}–*H*), 7.27 (dd, 1H, J(5′,6′) = 8.0 Hz, J (4′,5′) = 7.7 Hz, $C_{5'}$–H), 7.39 (ddd, 1H, J(5′,6′) = 8.0 Hz, J (2′,6′) = 1.8 Hz, J(4′,6′) = 1.2 Hz, $C_{6'}$–H), 7.49 (ddd, 1H, J (4′,5′) = 7.7 Hz, J(2′,4′) = 1.6 Hz, J(4′,6′) = 1.2 Hz, $C_{4'}$–H), 7.58 (dd, 1H, J(3,4) = 8.6 Hz, J(4,6) = 2.2 Hz, C_4–H), 7.70 (dd, 1H, J (2′,6′) = 1.8 Hz, J(2′,4′) = 1.6 Hz, $C_{2'}$–H), 8.83 (d, 1H, J (4,6) = 2.2 Hz, C_6–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.3 ($SO_2CH_2CH_3$), 49.6 (SO_2CH_2), 56.2 (OCH_3), 110.8 (C_3), 115.8 (C_6), 121.4 and 122.0 and 122.2 (C_4, $C_{3'}$ and C_{4*}), 123.9 ($C_{6'}$), 124.9 ($C_{1'}$), 128.5 ($C_{4'}$), 129.6 and 129.98 and 130.0 (C_1, $C_{2'}$, and $C_{5'}$), 142.5 (C_{5*}), 151.4 (C_2), 156.2 (C_{2*}). *Anal.* Calcd for $C_{18}H_{17}BrN_2O_4S$ (437.31) C, 49.44; H, 3.92; Br, 18.27; N, 6.41; S, 7.33. Found: C, 49.52; H, 4.01; Br, 18.21; N, 6.37; S, 7.26.

5-(3,5-Dibromophenyl)-*N*-[5-(ethylsulfonyl)-2-methoxyphenyl] oxazole-2-amine (XXb). This compound was obtained by method A, 100.0 mg (0.19 mmol, 19.4%), as a pale yellow powder. mp 231.0–233.0 °C [EA/Hex]. IR ν (solid): 3414 (m, NH), 3026 (w), 2854 (w), 1601 (s), 1574 (s), 1549 (s), 1527 (m), 1429 (m), 1308 (s, S=O), 1264 (s), 1123 (s, S=O), 1020 (s), 737 (m) cm^{-1}.^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, 3H, J = 7.4 Hz, –CH_3), 3.17 (q, 2H, J = 7.4 Hz, –CH_2–), 4.03 (s, 3H, –OCH_3), 7.01 (d, 1H, J (3,4) = 8.6 Hz, C3–H), 7.23 (s, 1H, C4*–H), 7.52 (t, 1H, J (2′,4′) = 1.6 Hz, C4′–H), 7.58 (dd, 1H, J(3,4) = 8.6, J (4,6) = 2.3 Hz, C4–H), 7.61 (d, 2H, J(2′,4′) = 1.6 Hz, C2′–H), 7.66 (br s, 1H, –NH–), 8.85 (d, 1H, J(4,6) = 2.3 Hz, C6–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.6 (–CH_3), 50.7 (–SO_2CH_2–), 56.3 (–OCH_3), 109.6 (C_3), 115.6 (C_6), 122.9 (C_{4*}), 123.5 ($C_{3'}$), 124.2 (C_4), 124.5 (C_1'), 128.4 ($C_{4'}$), 130.9 ($C_{2'}$), 131.0 (C_1), 132.5 (C_5), 142.6 (C_{5*}), 150.5 (C_2), 155.6 (C_{2*}). *Anal.* Calcd for $C_{18}H_{16}Br_2N_2O_4S$ (516.20): C, 41.88; H, 3.12; Br, 30.96; N, 5.43; S, 6.21. Found: C, 41.62; H, 2.86; Br, 31.32; N, 4.93; S, 6.03.

1-[2-(3,5-Dibromophenyl)-2-oxoethyl]-3-[5-(ethylsulfonyl)-2-methoxyphenyl]urea (XXIb). This compound was obtained by method A, 139.0 mg (0.26 mmol, 26.0%), as a yellow powder. mp 149.0–153.0 °C [EA/Hex]. IR ν (solid): 3325 (m, NH), 3072 (w), 2940 (w), 1744 (s, C=O), 1654 (s, C=O), 1594 (s), 1524 (s), 1411 (s), 1370 (m), 1305 (s, S=O), 1260 (s), 1228 (s), 1130 (s, S=O), 1084 (m), 1019 (w), 836 (w), 815 (w), 774 (w), 738 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.21 (t, 3H, J = 7.5 Hz, –CH_3), 3.08 (q, 2H, J = 7.5 Hz, –CH_2–), 3.87 (s, 3H, –OCH_3), 4.70 (d, 2H, J(NH,CH_2) = 4.5 Hz, CO–NH–CH_2), 6.11 (t, 1H, J (NH,CH_2) = 4.5 Hz, CO–*NH*–CH_2), 7.02 (d, 1H, J (3,4) = 8.7 Hz, C_3–H), 7.58 (t, 1H, J(2′,4′) = 1.6 Hz, $C_{4'}$–H), 7.67 (d, 2H, J(2′,4′) = 1.7 Hz, $C_{2'}$–H), 7.83 (dd, 1H, J (3,4) = 8.7, J(4,6) = 2.3 Hz, C_4–H), 7.95 (d, 1H, J(4,6) = 2.3 Hz, C_6–H), 8.13 (s, 1H, Ar–*NH*–CO). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.6 ($SO_2CH_2CH_3$), 45.8 (CH_2CO), 50.6 ($SO_2CH_2CH_3$), 56.3 (OMe), 111.0 (C_3), 116.2 (C_6), 121.2 (C4), 123.4 ($C_{3'}$), 128.3 ($C_{4'}$), 130.1 (C_1), 130.8 ($C_{2'}$), 134.3 (C_5), 139.1 ($C_{1'}$), 154.3 (C_2), 156.3 (NH–*CO*–NH), 189.3 (CH_2CO). *Anal.* Calcd for $C_{18}H_{18}Br_2N_2O_5S$ (534.22): C, 40.47; H, 3.40; Br, 29.91; N, 5.24; S, 6.00. Found: C, 40.27; H, 3.19; Br, 29.89; N, 5.41; S, 6.10.

1-[2-(3-Bromo-5-methoxyphenyl)-2-oxoethyl]-3-[5-(ethylsulfonyl)-2-methoxyphenyl]urea (XXIc). This compound was obtained by method A, 49.0 mg (0.10 mmol, 10.1%), as a white powder.

mp 161.0–164.0 °C [EA/Hex] IR ν (solid): 3364 (m, NH), 2942 (w), 1683 (s, C=O), 1659 (m), 1588 (m), 1540 (m), 1495 (m), 1415 (m), 1295 (s, S=O), 1261 (s), 1204 (m), 1121 (s, S=O), 1084 (m), 1046 (m), 1011 (m), 920 (w), 817 (m), 718 (m), 681 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, 3H, *J* (CH_3,CH_2) = 7.4 Hz, $SO_2CH_2CH_3$). 3.13 (q, 2H, *J*(CH_3, CH_2) = 7.4 Hz, $SO_2CH_2CH_3$), 3.86 (s, 3H, C_5–*OMe*), 3.95 (s, 3H, C_2–*OMe*), 4.78 (d, 2H, *J*(NH,CH_2) = 4.4 Hz, CONHCH_2), 5.92 (t, 1H, *J*(NH,CH_2) = 4.4 Hz, CO*NH*CH_2), 6.94 (d, 1H, *J* (3,4) = 8.6 Hz, C_3–H), 7.28 (s, 1H, Ar–*NH*–CO), 7.30 (dd, 1H, *J*(4′,6′) = 2.4 Hz, *J*(2′,4′) = 1.6 Hz, $C_{4'}$–H), 7.42 (dd, 1H, *J* (4′,6′) = 2.4 Hz, *J*(2′,6′) = 1.6 Hz, C_6–H), 7.55 (dd, 1H, *J* (3,4) = 8.6 Hz, *J*(4,6) = 2.3 Hz, C_4–H), 7.70 (dd, 1H, *J*(2′,4′) = 1.6 Hz, *J* (2′,6′) = 1.6 Hz, C_2–H), 8.67 (d, 1H, *J*(4,6) = 2.3 Hz, C_6–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.6 ($SO_2CH_2CH_3$), 47.4 ($COCH_2$), 50.5 ($SO_2CH_2CH_3$), 55.9 (OCH_3), 56.1 (OCH_3), 109.5 (C_3), 111.9 ($C_{3'}$), 117.9 (C_6), 122.94 and 122.88 (C_4 and $C_{2'}$), 123.5 and 123.3 ($C_{4'}$ and $C_{6'}$), 129.4 (C_5), 130.3 (C_1), 136.7 ($C_{1'}$), 151.3 (C_2), 154.4 (NH*CO*NH), 160.6 ($C_{5'}$), 194.1 (*CO*CH_2). *Anal*. Calcd for $C_{19}H_{21}BrN_2O_6S$ (485.35): C, 47.02; H, 4.36; Br, 16.46; N, 5.77; S, 6.61. Found: C, 46.86; H, 4.23; Br, 16.57; N, 5.71; S, 6.84.

5-[3-Bromo-4-(methoxymethoxy)phenyl]-N-[5-(ethylsulfonyl)-2-methoxyphenyl]oxazole-2-amine (XXd). This compound was obtained by method A, 154.0 mg (0.31 mmol, 31.0%), and by method B, 199.0 mg (0.40 mmol, 40.0%), as a white powder. mp 176.0–178.0 °C [EA/Hex]. IR ν (solid): 3364 (m, NH), 3007 (w), 2884 (w), 1604 (s), 1570 (s), 1539 (s), 1407 (m), 1288 (s, S=O), 1264 (s), 1119 (s, S=O), 1045 (m), 1021 (s), 747 (m, C–Br) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.12 (t, 3H, *J* = 7.4, $SO_2CH_2CH_3$), 3.20 (q, 2H, *J* = 7.4, $SO_2CH_2CH_3$), 3.98 (s, 3H, OCH_3), 3.43 (s, 3H, CH_2OCH_3), 5.33 (s, 2H, OCH_2O), 7.27 (d, 1H, *J*(3′,4′) = 8.7 Hz, $C_{3'}$–H), 7.30 (d, 1H, *J*(5,6) = 8.7 Hz, C_5–H), 7.50 (dd, 1H, *J* (3′,4′) = 8.7 Hz, *J*(4′,6′) = 2.2 Hz, $C_{4'}$–H), 7.52 (s, 1H, (C_{4*}–H), 7.57 (dd, 1H, *J*(5,6) = 8.7 Hz, *J*(2,6) = 2.1 Hz, C_6–H), 7.87 (d, 1H, *J*(2,6) = 2.1 Hz, C_2–H), 8.78 (d, 1H, *J*(4′,6′) = 2.2 Hz, $C_{6'}$–H), 9.75 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.3 ($SO_2CH_2CH_3$), 49.6 (SO_2CH_2), 55.9 (CH_2OCH_3), 56.2 (OCH_3), 94.5 (OCH_2O), 110.7 (C_3), 112.5 ($C_{3'}$), 115.5 (C_6), 116.6 ($C_{5'}$), 122.2 and 122.0 (C_4 and C_{4*}), 123.2 and 123.1 ($C_{6'}$ and $C_{1'}$), 127.1 ($C_{2'}$), 128.6 (C_5), 130.0 (C_1), 142.6 (C_{5*}), 151.3 (C_2), 152.0 ($C_{4'}$), 155.7 (C_{2*}). *Anal*. Calcd for $C_{20}H_{21}BrN_2O_6S$ (497.36) C, 48.30; H, 4.26; Br, 16.07; N, 5.63; S, 6.45. Found: C, 48.15; H, 4.23; Br, 15.99; N, 5.71; S, 6.84.

1-{2-[3-Bromo-4-(methoxymethoxy)phenyl]-2-oxoethyl}-3-[5-(ethylsulfonyl)-2-methoxy-phenyl]urea (XXId). This compound was obtained by method A, 149.0 mg (0.29 mmol, 28.9%), and by method B, 77.0 mg (0.15 mmol, 14.9%) in form of yellow crystals. mp 171.0–176.0 °C [EA/Hex]. IR ν (solid): 3298 (m, NH), 2982 (w), 1679 (w), 1608 (m), 1530 (m), 1475 (m), 1402 (m), 1291 (s, S=O), 1260 (s), 1196 (m), 1119 (s, S=O), 1080 (m), 1045 (m), 1008 (m), 815 (m), 711 (m), 663 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.08 (t, 3H, *J* = 7.3 Hz, $SO_2CH_2CH_3$), 3.14 (q, 2H, *J* = 7.3 Hz, $SO_2CH_2CH_3$), 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.76 (d, 2H, *J*(CH_2,NH) = 5.3 Hz, $COCH_2NH$), 7.22 (d, 1H, *J* (3,4) = 8.7 Hz, C3–H), 7.27 (d, 1H, *J*(5′,6′) = 8.7 Hz, $C_{5'}$–H), 7.42 (dd, 1H, *J*(3,4) = 8.7 Hz, *J*(4,6) = 2.3 Hz, C_4–H), 7.43 (t, 1H, *J*(NH,CH_2) = 5.3 Hz, NH), 8.05 (dd, 1H, *J*(5′,6′) = 8.7 Hz, *J*(2′,6′) = 2.1 Hz, $C_{6'}$–H), 8.17 (d, 1H, *J*(2′,6′) = 2.1 Hz, $C_{2'}$–H), 8.64 (d, 1H, *J*(4,6) = 2.3 Hz, C_6–H),8.68 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 7.4 ($SO_2CH_2CH_3$), 46.4 (C=OCH_2), 49.7 ($SO_2CH_2CH_3$), 56.3 (OCH_3), 56.8 (OCH_3), 110.6 (C_3), 111.0 ($C_{3'}$), 112.5 ($C_{5'}$), 116.6 (C_6), 121.6 (C_4), 128.9 (C_5), 129.6 ($C_{6'}$), 130.0 and 129.9 ($C_{1'}$ and C_1), 132.5 ($C_{2'}$), 151.0 (C_2), 155.1 (NH–*C*=*O*), 159.4 ($C_{4'}$–O), 193.7 (CH_2C=*O*). *Anal*. Calcd for $C_{20}H_{23}BrN_2O_7S$ (515.37) C, 46.61; H, 4.50; Br, 15.50; N, 5.44; S, 6.22. Found: C, 46.64; H, 4.39; Br, 15.45; N, 5.39; S, 6.17.

N-[5-(Ethylsulfonyl)-2-methoxyphenyl]-5-methyloxazole-2-amine (XXg). This compound was obtained by method A, 80 mg (0.27 mmol, 27.0%), in form of orange crystals. mp 149.0–150.0 °C [EtOH] IR ν (solid): 3422 (m, NH), 3089 (m, C–H), 2942 (w), 1639 (m), 1621(m), 1593(m), 1579(w), 1534 (m), 1461 (s), 1419 (m), 1346 (s), 1297 (s, S=O), 1261 (s), 1132 (s, S=O), 1014 (m), 838 (m), 743 (w), 717 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.10 (t, 3H, *J* = 7.2 Hz, CH_3), 2.24 (d, 3H, *J*(4*,CH_3) = 1.3 Hz, C_{5*}–CH_3), 3.17 (q, 2H, *J* = 7.2 Hz, CH_2), 3.94 (s, 3H, OMe), 6.67 (q, 1H, *J*(4*, CH_3) = 1.3 Hz, C_{4*}–H), 7.22 (d, 1H, *J*(3,4) = 8.4 Hz, C_3–H), 7.44 (dd, 1H, *J*(4,6) = 8.4 Hz, *J*(3,4) = 2.2 Hz, C_4–H), 8.75 (d, 1H, *J*(4,6) = 2.2 Hz, C_6–H), 9.37 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.2 ($SO_2CH_2CH_3$), 10.3 (C5*–CH_3), 49.6 ($SO_2CH_2CH_3$), 56.1 (OMe), 110.5 (C_3), 114.9 (C_6), 121.5 (C_{4*}), 121.6 (C_4), 129.9 and 129.1 (C_1 and C_5), 141.7 (C_{4*}), 151.0 (C_2), 154.9 (C_{2*}). *Anal*. Calcd for $C_{13}H_{16}N_2O_4S$ (296.34): C, 52.69; H, 5.44; N, 9.45; S, 10.82. Found: C, 52.88; H, 5.32; N, 9.28; S, 10.62.

Ethyl 2-{2-[5-(ethylsulfonyl)-2-methoxyphenylamino]oxazol-5-yl}acetate (XXh). This compound was obtained by method A, 92.0 mg (0.25 mmol, 25.0%), as yellow powder. mp 235.0–237.0 °C [EA/Hex] IR ν (solid): 3334 (m, NH), 3089 (w), 2976 (w), 1736 (s, C=O), 1614 (m), 1599 (s), 1578 (s), 1541 (m), 1487 (m), 1432 (m), 1296 (s, S=O), 1121 (s, S=O), 1084 (m), 1022 (m), 734 (w), 719 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.00–1.30 (m, 6H, 2x CH_3), 3.15 (q, 2H, *J* = 7.2 Hz, SO_2CH_2), 4.00 (s, 3H, OCH_3), 4.21 (q, 2H, *J* = 7.1 Hz, OCH_2), 6.79 (t, 1H, *J*(4*,CH_2) = 1.0 Hz, C_{4*}–H), 6.98 (d, 1H, *J*(3,4) = 8.5, C_3–H), 7.41 (bs, 1H, NH), 7.54 (dd, 1H, *J*(3,4) = 8.5 Hz, *J* (4,6) = 2.2 Hz, C_4–H), 8.81 (d, 1H, *J*(4,6) = 2.2 Hz, C_6–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.5 ($SO_2CH_2CH_3$), 14.1 ($COOCH_2CH_3$), 31.6 ($COCH_2$), 50.6 ($SO_2CH_2CH_3$), 56.2 (OCH3), 61.5 ($COOCH_2CH_3$), 109.4 (C_3), 115.1 (C_6), 122.3 (C_4), 124.7 (C_{5*}), 129.0 (C_5), 130.8 (C_1), 138.7 (C_{5*}), 150.4 (C_2), 155.2 (C_{2*}), 168.8 (CO). *Anal*. Calcd for $C_{16}H_{20}N_2O_6S$ (368.40): C, 52.16; H, 5.47; N, 7.60; S, 8.70 Found: C, 52.41; H, 5.49; N, 7.44; S, 8.59.

Ethyl 2-Aminooxazole-5-carboxylate (20). A mixture of 100.0 mg (1.67 mmol, 1.00 mol eq) of urea (**7**), 250.0 mg (1.67 mmol, 1.00 mol eq) of ethyl 2-chloro-3-oxopropionate (**16**) in 2 mL of water was heated at 100 °C for 1.5 h. The pH of the reaction mixture was set up to 7 by 10% aq solution of $NaHCO_3$, and the mixture was extracted with EA (4 × 3 mL). Combined organic layer was dried over Na_2SO_4 and filtered off, and the solvent removed by RVE. The product was obtained, 166.0 mg (1.06 mmol, 63.7%), as a yellow solid. mp 153.0–154.0 °C [EA] IR ν (solid): 3201 (s, NH), 3154 (m, NH), 2998 (m), 1741 (s, C=O), 1551 (s), 1424 (m), 1112 (m) cm^{-1}.^1H NMR (300 MHz, DMSO-d_6) δ: 1.35 (t, 3H, *J* = 7.2 Hz, CH_2CH_3), 4.30 (q, 2H, *J* = 7.2 Hz, CH_2CH_3), 5.37 (s, 2H, NH_2), 7.46 (s, 1H, C_4–H) [33]. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 156.0 (C=O), 152.3 (C_2), 140.5 (C_5), 132.8 (C_4), 61.6 (CH_2), 14.0 (CH_3). *Anal*. Calcd for $C_6H_6ClNO_3$ (175.57): C,

41.05; H, 3.44; Cl, 20.19; N, 7.98. Found: C, 40.89; H, 3.52; Cl, 20.11; N, 7.85.

1-(5-(Ethylsulfonyl)-2-methoxyphenyl)urea (21). Recently, we have described the synthesis of 5-(ethylsulfonyl)-2-methoxyaniline (**19a**) from commercial 4-methoxybenzenesulfonyl chloride (or anisol) [33]. 1-(5-(Ethylsulfonyl)-2-methoxyphenyl)]urea (**21**) was prepared by mixing a solution of 300.0 mg of KCNO (3.70 mmol, 1.28 mol eq) in 1 mL of water with a suspension of 620.0 mg of aniline **19a** (2.90 mmol, 1.00 mol eq) in 3 mL of 1*M* HCl. The mixture was stirred for 30 min at rt while the product was precipitating. The product was filtered off and washed with cold water and dried at low pressure. We obtained 203.0 mg (1.68 mmol, 57.8%) of pale beige powder. mp 198.0–199.1 °C [EA] *Anal*. Calcd for $C_{10}H_{14}N_2O_4S$ (258.29): C, 46.50; H, 5.46; N, 10.85; S, 12.41. Found: C, 46.39; H, 5.51; N, 10.78; S, 12.29. IR ν (solid, cm^{-1}): 3493 (m, N–H), 3280 (m, N–H), 3190 (m, N–H), 3012 (m, C–H), 1706 (s, C=O), 1663 (s), 1595 (s), 1534 (s), 1304 (s, S=O), 1263 (s), 1130 (s, S=O), 815 (m), 708 (m). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.09 (t, 3H, J = 7.2 Hz, $SO_2CH_2CH_3$), 3.15 (q, 2H, J = 7.2 Hz, $SO_2CH_2CH_3$), 3.95 (s, 3H, OCH_3), 6.39 (bs, 2H, NH_2), 7.20 (d, 1H, J(3,4) = 8.6 Hz, C_3–H), 7.40 (dd, 1H, J (3,4) = 8.6 Hz, J(4,6) = 2.3 Hz, C_4–H), 8.26 (bs, 1H, NH), 8.66 (d, 1H, J(4,6) = 2.3 Hz, C_6–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.3 ($SO_2CH_2CH_3$), 49.6 ($SO_2CH_2CH_3$), 56.2 (OCH_3), 110.4 (C_3), 116.3 (C_6), 121.3 (C_4), 129.9 (C_1), 130.0 (C_5), 150.8 (C=O), 155.7 (C_2).

4-(3-Bromophenyl)-*N*-[5-(ethylsulfonyl)-2-methoxyphenyl] oxazole-2-amine (23). A suspension of 130.0 mg (0.50 mmol, 1.00 mol eq) of 5-(ethylsulfonyl)-2-methoxyphenylurea (**22**) and 140.0 mg (0.50 mmol, 1.00 mol eq) of α,3-dibromoacetophenone (**22**) was heated to reflux in 2 mL of ethanol within 24 h. After reaction completion, the solvent was removed by evaporation, and the product was obtained by column chromatography on silica (EA/Hex = 2 : 1) in the form of a yellow powder. The product was purified by crystallization in ethanol obtaining 103.0 mg (0.24 mmol, 46.8%) of pale yellow crystals. mp 206.0–208.0 °C [EtOH] IR ν (solid): 3404 (m, N–H), 3096 (m), 1747 (w), 1261 (s), 1230 (s, S=O), 1129 (s, S=O), 1108 (s), 712 (s) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 0.95 (t, 3H, CH_2CH_3), 3.18 (q, 2H, CH_2CH_3), 3.91 (s, 3H, OCH3), 5.85 (s, 1H, C_{4*}–H), 7.28 (dd, 1H, J(4′,6′) = 7.8 Hz, J(5′,6′) = 7.9 Hz, $C_{5'}$–H), 7.29 (d, 1H, J(3,4) = 8.6 Hz, C_3–H), 7.40 (ddd, 1H, J(4′,5′) = 7.9 Hz, J(4′,6′) = 1.9 Hz, J(2′,4′) = 1.7 Hz, $C_{4'}$–H), 7.49 (ddd, 1H, J (5′,6′) = 7.9 Hz, J(4′,6′) = 1.9 Hz, J(2′,6′) = 1.6 Hz, $C_{6'}$–H), 7.61 (dd, 1H, J(2′,6′) = 1.7 Hz, J(2′, 4′) = 1.6 Hz, $C_{2'}$–H), 7.73 (dd; 1H, J(3,4) = 8.6 Hz, J(3,6) = 2.3 Hz, C_4–H), 7.90 (d, 1H, J (4,6) = 2.3 Hz, C_6–H), 11.58 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.3 (CH_3), 49.4 (CH_2), 56.5 (OCH_3), 65.5 (C_{5*}), 113.0 (C_3), 121.8 (C_6), 124.1 (C_4), 127.0 ($C_{3'}$), 128.8 ($C_{6'}$), 128.9 ($C_{5'}$), 129.6 ($C_{4'}$), 130.6 ($C_{2'}$), 130.8 ($C_{1'}$), 131.6 (C_5), 136.1 (C_1), 154.9 (C_{4*}), 158.4 (C_2), 171.7 (C_{2*}). *Anal*. Calcd for $C_{18}H_{17}BrN_2O_4S$ (437.31): C 49.44%; H 3.92%; Br 18.27%; N 6.41%; S 7.33%. Found: C 48.78% H 4.18%; N 6.11%; S 7.07%.

Ethyl 2-[5-(Ethylsulfonyl)-2-methoxyphenylamino]oxazole-5-carboxylate (24). To 1.11 g (7.37 mmol, 1.03 mol eq) of ethyl 2-chloropropionate (**16**) a solution of 1.85 g (7.16 mmol, 1.00 mol eq) of 5-(ethylsulfonyl)-2-methoxyphenylurea (**21**) in 26 mL of ethanol was added. The reaction mixture was refluxed overnight. Then, the solvent was removed on RVE, and the solid material (2.89 g) was purified by FLC on silica gel (EA/Hex 1 : 1). The product, 190.0 mg (0.54 mmol, 7.5%), was obtained as a white solid. mp 141.0–143.0 °C [EA/Hex]. IR ν (solid): 3477 (w, NH), 2980 (w), 2944 (w), 1702 (m), 1610 (s), 1570 (s), 1492 (m), 1424 (w), 1373 (m), 1321 (m, S=O), 1265 (m), 1206 (w), 1140 (m), 1122 (s, S=O, 1084 (m), 1014 (m), 980 (w), 920 (w), 794 (w), 722 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.11 (t, 3H, J = 7.3 Hz, $SO_2CH_2CH_3$), 1.29 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 3.20 (q, 2H, J = 7.3 Hz, $SO_2CH_2CH_3$), 3.94 (s, 3H, OCH_3), 4.29 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 7.29 (d, 1H, J(3,4) = 8.7 Hz, C_3–H), 7.57 (dd, 1H, J(3,4) = 8.7 Hz, J(4,6) = 2.3 Hz, C_4–H), 8.66 (d, 1H, J (4,6) = 2.3 Hz, C_6–H), 7.88 (s, 1H, C_{4*}–H), 10.32 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.2 ($SO_2CH_2CH_3$), 14.1 ($COOCH_2CH_3$), 49.6 (SO_2CH_2), 56.2 (OCH_3), 60.5 ($COOCH_2$), 111.2 (C_3), 117.4 (C_6), 123.7 (C_4), 129.9 and 127.7 (C_{4*} and C_5), 135.9 and 135.6 (C_1 and C_{5*}), 152.3 (C_2), 157.1 (C_{2*}), 158.7 (C=O). MS: 354 (100, M+), 335 (7), 323 (14), 309 (10), 295 (5), 281 (8), 261 (8), 242 (5), 225 (15), 215 (10), 196 (8), 155 (8), 133 (10), 124 (7), 91 (5), 76 (7). *Anal*. Calcd for $C_{15}H_{18}N_2O_6S$ (354.38): C, 50.84; H, 5.12; N, 7.90; S, 9.05. Found: C, 50.63; H, 5.30; N, 7.79; S, 9.27.

Ethyl 2-chloro-3-(3-(5-(ethylsulfonyl)-2-methoxyphenyl) ureido)acrylate (25). This compound was obtained, 1030 mg (2.64 mmol, 36.8%), as a white solid compound. mp 204.0–206.0 ° C [MeOH]. IR ν (solid): 3334 (m, NH), 3021 (m) 1719 (s, C=O), 1644 (m), 1596 (m), 1535 (m), 1377 (s, S=O), 1269 (m), 1118 (s, S=O), 723 (m) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.09 (t, 3H, $SO_2CH_2CH_3$, J = 7.2 Hz), 1.25 (t, 3H, $COOCH_2CH_3$, J = 7.2 Hz), 3.19 (q, 2H, $SO_2CH_2CH_3$, J = 7.2 Hz), 4.00 (s, 3H, OCH_3), 4.21 (q, 2H, $COOCH_2CH_3$, J = 7.2 Hz), 7.31 (d, 1H, J(3,4) = 8.7 Hz, C_3–H), 7.56 (dd, 1H, J (3,4) = 8.7 Hz, J (4,6) = 2.4 Hz, C_4–H), 8.20 (d, 1H, J (NH,*CH*) = 11.4 Hz, NH*CH*), 8.64 (d, 1H, J(4,6) = 2.4 Hz, C_6–H), 9.45 (s, 1H, NH), 9.99 (d, 1H, J (*NH*,CH) = 11.4 Hz, *NH*CH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.1 ($SO_2CH_2CH_3$), 13.9 ($COOCH_2CH_3$), 49.7 ($SO_2CH_2CH_3$), 56.3 (OCH_3), 61.5 ($COOCH_2CH_3$), 100.5 (*C*ClCOOEt), 111.1 (C_3), 117.5 (C_6), 123.8 (C_4), 127.5 (C_5), 129.7 (C_1), 133.7 (*CH*NH), 150.4 (NH*CO*NH), 151.7 (C_2), 162.7 (*COO*Et). GC-MS: Two different decomposition fragment combinations, four peaks in GC: 241 + 149 = 390 and 175 + 215 = 390; fragment 1 *m/z* (%): 241 (100, F+), 212 (84), 196 (34), 164 (48), 148 (70), 133 (10), 120 (29), 105 (5), 92 (11), 77 (25), 65 (8), 51 (7). Fragment 2 MS *m/z* (%): 149 (73, F+), 134 (4), 121 (52), 104 (100), 103 (100), 76 (45), 49 (8). Fragment 3 MS *m/z* (%): 175 (45, F+), 147 (80), 130 (100), 119 (40), 104 (28), 91 (8), 74 (35), 60 (3), 45 (9). Fragment 4 MS *m/z* (%): 215 (100, F+), 200 (11), 185 (10), 170 (11), 155 (10), 138 (5), 124 (39)m 122 (65), 107 (10), 79 (11), 77 (11), 52 (10).

Ethyl 2-chloro-3-[5-(ethylsulfonyl)-2-methoxyphenylamino] acrylate (26). This compound was obtained, 370.0 mg (1.06 mmol, 14.9%), as white solid compound. mp 128.0–130.0 ° C [EtOH] IR ν (solid): 3390 (w, N-H), 3032 (m, arom. C–H), 1703 (s, C=O), 1641 (s), 1597 (m), 1311 (s, S=O), 1252 (s), 1125 (s, S=O), 791 (s), 714 (m, C–Cl) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.09 (t, 3H, J = 7.5 Hz, $SO_2CH_2CH_3$), 1.26 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 3.31 (q, 2H, J = 7.5 Hz, $SO_2CH_2CH_3$), 3.99 (s, 3H, OCH_3), 4.20 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 7.30 (d, 1H, J(3,4) = 8.4 Hz, C_3–H), 7.54 (dd, 1H, J (3,4) = 8.4 Hz, J(4,6) = 2.1 Hz, C_4–H), 7.84 (d, 1H, J (4,6) = 2.1 Hz, C_6–H), 7.87 (d, 1H, J(CH,*NH*) = 13.2 Hz, CH*NH*), 8.38 (d, 1H, J(CH,*NH*) = 13.2 Hz, *CH*NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.5 ($SO_2CH_2CH_3$), 14.7 ($COOCH_2CH_3$), 49.8

($SO_2CH_2CH_3$), 57.1 (OCH_3), 61.5 ($COOCH_2CH_3$), 97.9 (*C*ClCOOEt), 112.2 (C_3), 114.9 (C_6), 124.2 (C_4), 129.8 (C_5), 130.8 (C_1), 137.2 (CHNH), 152.4 (C_2), 163.6 (*COO*Et). MS *m/z* (%): 347 (100, M+), 302 (8), 274 (4), 266 (25), 256 (10), 226 (56), 208 (10), 194 (5), 180 (9), 166 (9), 180 (10), 166 (9), 138 (8), 102 (5), 79 (10), 63 (3).

1-[2-(3-Bromo-5-nitrophenyl)-2-oxoethyl]pyrimidin-2(*1H*)-one (28). To a suspension of 288.0 mg (2.17 mmol, 2.00 mol eq) of 2-hydroxypyrimidine hydrochloride (**18**) in 5 mL of acetone, 599 mg (4.34 mmol, 4.00 mol eq) of K_2CO_3 was added at rt. After 10 min, a solution of 350 mg (1.08 mmol, 1.00 mol eq) of 2-bromo-1-(3-bromo-5-nitrophenyl)ethanone (**27**) in 2 mL of acetone was added. The reaction mixture was stirred at rt for 2 days. Acetone was evaporated on RVE, and the solid material was washed with water (3 × 5 mL), ethanol (5 mL), and diethyl ether (10 mL). The solid product was dried by HV, gaining 314.0 mg (0.93 mmol, 86.1%) of a light brown powder. mp 227.0–230.0 °C [Et_2O] IR ν (solid): 3082 (w), 2918 (w), 1658 (s, C=O), 1613 (m), 1550 (s, NO_2), 1393 (m), 1347 (s, NO_2), 1221 (m), 1084 (w), 887 (m), 735 (m), 665 (w, C–Br) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 5.60 (s, 2H, CH_2), 6.55 (dd, 1H, J(4*,5*) = 6.4 Hz, J(4*,6*) = 4.2 Hz, C_{5*}–H), 8.14 (dd, 1H, J(4*,5*) = 6.4 Hz, J(4*,6*) = 2.6 Hz, C_{4*}–H), 8.64–8.76 (m, 4H, C_2–H, C_4–H, C_6–H, and C_{6*}–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 56.6 (CH_2), 104.1 (C_{5*}), 121.5 (C_6), 123.0 (C_3), 130.8 (C_4), 136.8 (C_1), 137.0 (C_2), 149.0 (C_5), 150.5 (C_{6*}), 155.6 (C_{2*}), 167.2 (C_{4*}), 190.7 (CO). *Anal*. Calcd for $C_{12}H_8BrN_3O_3$ (338.11): C 42.63; H 2.38; Br 23.63; N 12.43. Found C 42.45; H 2.31; Br 23.71; N 12.51.

2-(3-Bromo-5-nitrophenyl)oxazolo[3,2-a]pyrimidin-4-ium perchlorate (29-ClO_4). Oleum 1.00 mL (4.81 mmol, 10.9 mol eq) (20% SO_3 w/w in conc. H_2SO_4) was added dropwise to 150.0 mg (0.44 mmol, 1.00 mol eq) of 1-[2-(3-bromo-5-nitrophenyl)-2-oxoethyl]pyrimidin-2(*1H*)-one (**29**) at 0 °C. The mixture was cooled until the whole solid material dissolved. Then, the solution was stirred at rt for 3 days. The reaction was quenched by 18 g of ice, and 370 µL (4.29 mmol, 9.8 mol eq) of $HClO_4$ (70%) was added dropwise that caused precipitation of the perchlorate salt **29-ClO_4**. The product was filtered off, washed with water, and dried at HV to yield 169.0 mg (0.40 mmol, 91.3%) as a brown powder. mp 228.0–231.0 °C [H_2O] IR ν (solid): 3084 (m), 2797 (w), 1755 (m), 1589 (m), 1521 (s, NO_2), 1499 (w), 1416 (w), 1346 (s, NO_2), 1223 (m), 1095 (m), 1034 (m), 885 (w), 768 (w), 735 (m, C–Br) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 8.23 (dd, 1H, J(5*,6*) = 6.5 Hz, J(6*,7*) = 4.7 Hz, C_{6*}–H), 8.66 (dd, 1H, J(2,6) = 1.8 Hz, J(2,4) = 1.7 Hz, C_2–H), 8.83 (dd, 1H, J(2,4) = 1.7 Hz, J(4,6) = 1.7 Hz, C_4–H), 8.87 (dd, 1H, J(2,6) = 1.8 Hz, J(4,6) = 1.7 Hz, C_6–H), 9.49 (dd, 1H, J(6*,7*) = 4.7 Hz, J(5*, 7*) = 1.9 Hz, C_{7*}–H), 9.62 (s, 1H, C_{3*}–H), 9.82 (dd, 1H, J(5*,6*) = 6.5 Hz, J(5*, 6*) = 1.9 Hz, C_{5*}–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 114.1 (C_{3*}), 118.6 and 117.5 (C_6 and C_{6*}), 123.5 (C_3), 126.7 (C_4), 134.0 (C_1), 136.7 (C_2), 142.9 (C_{5*}), 148.2 (C_5), 149.3 (C_{2*}), 155.7 (C_{9*}), 163.7 (C_{7*}). *Anal*. Calcd for $C_{12}H_7BrClN_3O_7$ (420.56): C, 34.27; H, 1.68; Br, 19.00; Cl, 8.43; N, 9.99. Found C, 33.95; H, 1.56; Br, 18.89; Cl, 8.33; N, 9.72.

5-(3-Bromo-5-nitrophenyl)oxazole-2-amine (30). Hydrazine hydrate 120 µL (2.35 mmol, 12.4 mol eq) was added drop wise to a solution of 80 mg (0.19 mmol, 1.00 mol eq) of 2-(3-bromo-5-nitrophenyl)oxazolo[3,2-a]pyrimidin-4-ium perchlorate (**29-ClO_4**) in 1.0 mL of acetonitrile. The mixture changed its color to orange-red and was heated to 100 °C until the orange-red color disappeared (~15 min). Afterward, 2.0 mL of water was added to the mixture that caused precipitation of the product **30**. The precipitate was too fine to be filtered off, and therefore, it was extracted with EA (3 × 5 mL). Combined organic layer was dried over Na_2SO_4 and filtered off, and the solvent was removed on RVE. The crude product was purified by FLC on silica gel (EA/Hex 1 : 1) yielding 39.0 mg (0.14 mmol, 72.2%) of bright orange solid **33**. mp 220.0–221.0 °C [EA/Hex] IR ν (solid): 3322 (m, NH_2), 3132 (m, NH_2), 1711 (s), 1660 (s), 1612 (s), 1584 (s). 1527 (s, NO_2), 1416 (s), 1378 (s), 1341 (s, NO_2), 1297 (m), 1169 (m), 1095 (w), 1048 (w), 994 (w), 962 (w), 880 (w), 737 (w) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 7.60 (bs, 2H, NH_2), 7.63 (s, 1H, C_{4*}–H), 8.09 (dd, 1H, J(2,4) = 1.7 Hz, J(2,6) = 1.6 Hz, C_2–H), 8.11 (dd, 1H, J(4,6) = 2.0 Hz, J(2,4) = 1.7 Hz, C_4–H), 8.15 (dd, 1H, J(4,6) = 2.0 Hz, J(2,6) = 1.6 Hz, C_6–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 114.6 (C_6), 122.4 (C_3), 122.5 (C_{4*}), 127.8 (C_4), 129.4 (C_2), 131.6 (C_1), 139.6 (C_{5*}), 149.1 (C_5), 162.5 (C_{2*}). *Anal*. Calcd for $C_9H_6BrN_3O_3$ (284.07): C 38.05; H 2.13; Br 28.13; N 14.79. Found: C 38.10; H 2.06; Br 28.11; N 14.69.

General procedure for the preparation of 2-chlorooxazoles (32 and 34). *t*-BuONO 0.23 mL (199 mg, 1.93 mmol, 1.50 mol eq) was added to a solution of 0.26 g (1.92 mmol, 1.50 mol eq) $CuCl_2$ abs in 3.0 mL of dry AN at rt. The mixture was stirred at 60 °C while a solution of the oxazole-2-amine (**31** or **33**) (1.28 mmol, 1.00 mol eq) in 2 mL of CH_3CN was added. Afterward, the reaction mixture was stirred at 80 °C for 2 days. It was cooled to rt, and 5 mL of EA, 3 mL of water, and 0.5 mL of conc. HCl were added. The mixture was stirred for another 15 min. The organic layer was separated, and the aqueous layer extracted with EA (3 × 5 mL). The combined organic layer was dried over Na_2SO_4 and filtered off, and the solvent removed on RVE.

Ethyl 2-chlorooxazole-5-carboxylate (32). This compound was obtained, 171.0 mg (0.97 mmol, 76.1%), as a light green oil [30]. IR ν (solid): 2985 (m), 1727 (s, C=O), 1588 (s), 1420 (m),1103 (m), 708 (m, C–Cl) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.30 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 4.33 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 8.08 (bs, 1H, C_4–H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 156.4 (C=O), 150.0 (C_2), 144.5 (C_5), 135.0 (C_4), 61.8 (CH_2), 14.1 (CH_3). *Anal*. Calcd for $C_6H_6ClNO_3$ (175.57): C, 41.05; H, 3.44; Cl, 20.19; N, 7.98. Found: C, 40.89; H, 3.52; Cl, 20.11; N, 7.85.

5-(3-Bromo-5-nitrophenyl)oxazol-2-chloride (34). This compound was obtained, 319.0 mg (1.05 mmol, 82.1%), as a brown solid. mp 168.0–172.0 °C [EA] IR ν (solid): 3087 (m), 2960 (m), 2907 (w), 1713 (m), 1705 (m), 1597 (w), 1532 (s, NO_2), 1434 (w), 1418 (w), 1345 (s, NO_2), 1259 (m), 1136 (w), 1089 (w), 1045 (m), 881 (m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.52 (s, 1H, C_{4*}–H), 8.05 (1H, dd, J(2,4) = 1.6 Hz, J(2,6) = 1.5 Hz, C_2–H), 8.34 (1H, dd, J(4,6) = 1.8 Hz, J(2,4) = 1.6 Hz, C_4–H), 8.37 (1H, dd, J(4,6) = 1.8 Hz, J(2,6) = 1.5 Hz, C_6–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 117.5 (C_6), 123.0 (C_{4*}), 149.9 and 149.1 (C_5 and C_{2*}), 125.9 (C_3), 127.6 (C_4), 129.4 (C_2), 132.1 (C_1), 137.6 (C_{5*}). *Anal*. Calcd for $C_9H_6BrClN_2O_3$ (303.50): C, 35.62; H, 1.33; Br, 26.33; Cl, 11.68; N, 9.23. Found: C, 35.28; H, 1.31; Br, 26.14; Cl, 11.53; N, 9.40.

General procedure of transformation of 2-chlorooxazoles to *N*-aryloxazole-2-amines (24 and 35). To a solution of 142.0 mg (0.66 mmol, 1.00 mol eq) of 5-(ethylsulfonyl)-2-methoxyaniline (**35**) in 12 mL of dry *i*-PrOH, 2-chlorooxazole (**32** or **34**) (0.66 mmol, 1.00 mol eq) was added at rt. The

reaction mixture was stirred at the same temperature for 5 days in case of **32** (**32** was decomposing over reaction time, all together 3 × 0.66 mmol of **32** was added within this time to ensure complete conversion of the starting aniline **35**) or for 14 days in case of **34**. After complete conversion of **35**, the solvent was removed on RVE, and the crude product purified by FLC on silica gel (Hex/EA).

Ethyl 2-[5-(Ethylsulfonyl)-2-methoxyphenylamino]oxazole-5-carboxylate (24). This compound was obtained, 180.0 mg (0.51 mmol, 77.0%), as a white solid. mp 142.0–143.0 °C [EA/Hex]. IR ν (solid): 3477 (w, NH), 2980 (w), 2944 (w), 1702 (m), 1610 (s), 1570 (s), 1492 (m), 1424 (w), 1373 (m), 1321 (m, S=O), 1265 (m), 1206 (w), 1140 (m), 1122 (s, S=O, 1084 (m), 1014 (m), 980 (w), 920 (w), 794 (w), 722 (m) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6) δ: 1.11 (t, 3H, J = 7.3 Hz, $SO_2CH_2CH_3$), 1.29 (t, 3H, J = 7.1 Hz, $COOCH_2CH_3$), 3.20 (q, 2H, J = 7.3 Hz, $SO_2CH_2CH_3$), 3.94 (s, 3H, OCH_3), 4.29 (q, 2H, J = 7.1 Hz, $COOCH_2CH_3$), 7.29 (d, 1H, J(3,4) = 8.7 Hz, C_3–H), 7.57 (dd, 1H, J(3,4) = 8.7 Hz, J(4,6) = 2.3 Hz, C_4–H), 8.66 (d, 1H, J(4,6) = 2.3 Hz C_6–H), 7.88 (s, 1H, C_{4*}–H), 10.32 (br s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 7.2 ($SO_2CH_2CH_3$), 14.1 ($COOCH_2CH_3$), 49.6 (SO_2CH_2), 56.2 (OCH_3), 60.5 ($COOCH_2$), 111.2 (C_3), 117.4 (C_6), 123.7 (C_4), 129.9 and 127.7 (C_{4*} and C_5), 135.9 and 135.6 (C_1 and C_{5*}), 152.3 (C_2), 157.1 (C_{2*}), 158.7 (C=O). *Anal.* Calcd for $C_{15}H_{18}N_2O_6S$ (354.38): C, 50.84; H, 5.12; N, 7.90; S, 9.05. Found: C, 50.71; H, 5.25; N, 7.81; S, 9.12.

5-(3-Bromo-5-nitrophenyl)-*N*-[5-(ethylsulfonyl)-2-methoxyphenyl] oxazole-2-amine (35). This compound was obtained, 212.0 mg (0.44 mmol, 66.7%), as a yellow solid after crystallization from CH_2Cl_2/Hex. mp 122.0–127.0 °C [CH_2Cl_2] IR ν (solid): 3357 (m, NH), 3082 (m), 2893 (m), 1738 (w), 1645 (s), 1599 (s), 1580 (s), 1531 (s, NO_2), 1505 (m), 1426 (w), 1346 (m, NO_2), 1304 (m, S=O), 1276 (m), 1143 (s, S=O), 1122 (s), 1093 (m), 1046 (w), 1013 (m), 928 (w), 881 (w) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (t, 3H, J = 7.4 Hz, $SO_2CH_2CH_3$), 3.19 (q, 2H, J = 7.4 Hz, $SO_2CH_2CH_3$), 4.06 (s, 3H, OCH_3), 7.05 (d, 1H, J(3,4) = 8.6 Hz, C_3–H), 7.40 (s, 1H, C_{4*}–H), 7.62 (dd, 1H, J(3,4) = 8.6 Hz, J(4,6) = 2.2 Hz, C_4–H), 7.83 (s, 1H, NH), 7.98 (dd, 1H, J(2′,4′) = 1.8 Hz, J(2′,6′) = 1.5 Hz, $C_{2'}$–H), 8.23 (dd, 1H, J(4′,6′) = 1.9 Hz, J(2′,4′) = 1.8 Hz, $C_{4'}$–H), 8.31 (dd, 1H, J(4′,6′) = 1.9 Hz, J(2′,6′) = 1.5 Hz, $C_{6'}$–H), 8.86 (d, 1H, J(4,6) = 2.2 Hz, C_6–H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 7.6 ($SO_2CH_2CH_3$), 50.7 ($SO_2CH_2CH_3$), 56.4 (OCH_3), 109.7 (C_3), 115.8 ($C_{6'}$), 116.3 (C_6), 123.5 and 123.3 (C_{4*} and C_4), 124.7 ($C_{3'}$), 128.2 ($C_{4'}$), 131.95 ($C_{2'}$), 131.07, 131.05 and 131.97 (C_1, C_5 and $C_{1'}$), 149.2 (C_{4*}), 150.62 and 150.59 (C_2 and $C_{5'}$), 156.1 (C_{2*}). *Anal.* Calcd for $C_{18}H_{16}BrN_3O_6S$ (482.31) C, 44.82; H, 3.34; Br, 16.57; N, 8.71; S, 6.65. Found: C, 44.98; H, 3.25; Br, 16.60; N, 8.63; S, 6.66.

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