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2-Aminooxazole as a Novel Privileged Scaffold in Antitubercular Medicinal Chemistry

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ABSTRACT: To obtain effective eradication of numerous infectious diseases such as tuberculosis, it is important to supply the medicinal chemistry arsenal with novel chemical agents. Isosterism and bioisosterism are widely known concepts in the field of early drug discovery, and in several cases, rational isosteric replacements have contributed to improved efficacy and physicochemical characteristics throughout the hit-to-lead optimization process. However, sometimes the synthesis of isosteres might not be as straightforward as that of the parent compounds, and therefore, novel synthetic strategies must be elaborated. In this regard, we herein report the evaluation of a series of N-substituted 4-phenyl-2-aminooxazoles that, despite being isosteres of a widely used nucleus such as the 2-aminothiazole, have been only seldom explored. After elaboration of a convenient synthetic strategy, a small set of 2-aminothiazoles and their 2-aminooxazole counterparts were compared with regard to antitubercular activity and physicochemical characteristics.

KEYWORDS: 2-Aminooxazole, 2-aminothiazole, bioisosterism, Buchwald−Hartwig coupling, isosterism
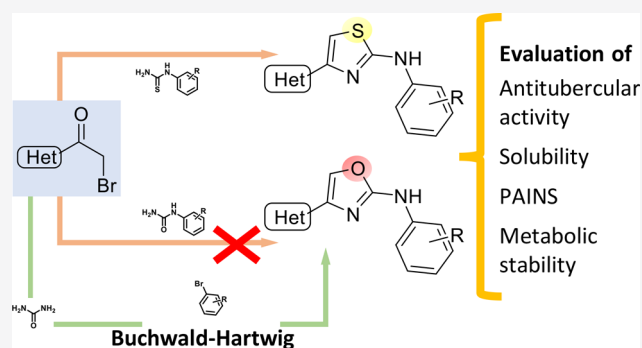
Chemotherapy is nowadays the only means to eradicate those bacterial infections for which an effective vaccine is not available. However, the emergence of antimicrobial resistance has significantly narrowed the scope of a number of chemotherapeutics, making them obsolete and sometimes devoid of efficacy.[1,2] In this regard, the exploitation of novel chemical tools to support the drug discovery process is highly desirable. This applies to tuberculosis (TB), which causes ill health among millions of people each year and ranks alongside HIV as the leading cause of death worldwide.[3−5] Specific medicinal chemistry efforts undertaken over a number of years have led to a nourished pipeline of novel chemical antitubercular entities, which are now in either the clinical or preclinical/hit-to-lead optimization phase.[6] With the aim to further enrich the antitubercular arsenal, in recent years we have developed a series of 2-aminothiazole derivatives (compounds **1−4**, Figure 1) endowed with strong antitubercular activity, irrelevant cytotoxicity toward eukaryotic cells, high selectivity toward other microorganisms, and little tendency to be substrate of *Mycobacterium tuberculosis* (*Mtb*) efflux pumps.[7−11]

Encouraged by these studies, and with the aim of further improving the antitubercular efficacy, we were interested in defining a reliable set of structure−activity relationships (SARs) for this series of molecules. First, we wanted to investigate whether the 2-aminothiazole moiety, which is
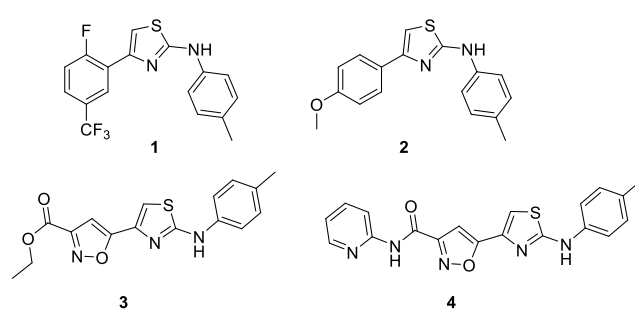

Figure 1. 2-Aminothiazoles with anti-TB activity.[7,10]

supposed to be the pharmacophore for molecules **1−4**, could be successfully replaced. The sulfur atom of the 2-aminothiazole can be easily oxidized, leading to metabolic inactivation of the molecule. In addition, 2-aminothiazoles, in some cases, have been identified as pan-assay interference compounds (PAINS),[12−14] and therefore, the evaluation of

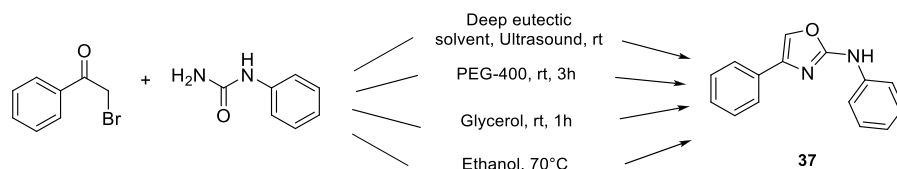ACS Publications | © 2020 American Chemical Society

Figure 2. Attempts to synthesize *N*,4-diphenyl-2-aminooxazole (**37**)[21−24]

different structural motifs might be worthwhile. The most obvious substitution of the 2-aminothiazole moiety is represented by the 2-aminooxazole,[15,16] where the sulfur atom of the thiazole ring is substituted by oxygen, a sulfur isostere.[16] In this regard, Hinsberg has extended the concept of isosterism and bioisosterism to heterocycles according to the "ring equivalence" theory, on the basis of which benzene, thiophene, pyridine, and furan can be considered ring equivalents. Moreover, the 2-aminooxazoles could possess some advantages over 2-aminothiazoles such as a decreased ClogP (and thus improved solubility) and a lower metabolism rate due to the lack of the oxidizable sulfur atom. These findings prompted us to plan the synthesis of a series of substituted 2-aminooxazoles to evaluate their biological activities in comparison with the corresponding 2-amino-thiazoles **1**−**4**. Although the synthesis of the oxazole core has been addressed by a number of groups,[17−19] the preparation of N-substituted 2-aminooxazoles has been only marginally considered. Surprisingly, the Hantzsch protocol,[20] a highly versatile method for the straightforward preparation of substituted 2-aminothiazoles starting from suitable *α*-bromo ketones and N-substituted thioureas, did not allow us to obtain 2-aminooxazoles when N-substituted ureas were used. Even more surprising was the fact that procedures to prepare 2-aminooxazole analogues presenting the same substituent pattern as our antitubercular 2-aminothiazoles (i.e., aromatic rings on C-4 and the nitrogen atom; Figure 1) have scarcely been reported in the scientific literature. For instance, the synthesis of a structure as simple as that of *N*,4-diphenyl-2-aminooxazole **37** (Figure 2) has rarely been reported,[21−24] and in all cases the synthetic procedures suffer from narrow feasibility and poor yields. In one case, upon reproduction of the conditions reported,[22] we failed to obtain the desired compound.

The poor reactivity of N-substituted ureas might be due to the lower nucleophilicity of the oxygen atom compared with the sulfur atom. However, this does not seem to apply to unsubstituted urea, which is reported to plainly react with different *α*-bromoacetophenones to give N-unsubstituted 2-aminooxazoles. In view of these findings, the development of a new and versatile synthetic strategy to efficiently obtain N-substituted 4-aryl-2-aminooxazoles might be of interest for the medicinal chemistry community.

Development of the Synthetic Method. Considering what is reported above, we evaluated the exploitation of an optimized two-step method based on (a) condensation of the proper *α*-bromoacetophenone with urea and (b) Buchwald−Hartwig cross-coupling of the 2-aminooxazole with an aryl halide. Finally, the versatility of the method was evaluated through the use of variously substituted *α*-bromoacetophe-nones and aryl halides. In this initial phase, *α*-bromo-4′-methylacetophenone (**5**) was used as the starting building block to react with urea (**6**) (Table 1). This reaction has been reported in six studies,[21,25−29] and the yield for the formation

Table 1. Optimization of the Condensation Reaction

entry	solvent	5:6 ratio	time	temp	yield (%)
I	EtOH	1:2	18 h	80 °C	0
II	EtOH	1:10	18 h	80 °C	0
III	PEG-400	1:2	18 h	20 °C	0
IV	CH$_3$CN	1:2	18 h	80 °C	0
V	CH$_3$CN	1:10	18 h	80 °C	0
VI	DME	1:10	18 h	80 °C	0
VII	DMSO	1:10	3 h	80 °C	0
VIII	DMF	1:2	8 h	80 °C	18
IX	DMF	1:10	3 h	80 °C	37
X	DMF	1:10	30 min	120 °C	45
XI	DMF	1:10	15 min	80 °C MW	53
XII	DMF	1:10	3 min	120 °C MW	56
XIII	NMP	1:10	15 min	80 °C MW	50
XIV	NMP	1:10	3 min	120 °C MW	45

of **7** was reported in only one case (21%).[25] For the first step, we focused our interest on optimizing parameters such as the solvent and the stoichiometric ratio and determining whether microwave (MW) irradiation is more efficient than conventional heating. With regard to the solvent, first attempts were made using acetonitrile, ethanol, dimethoxyethane (DME), and PEG-400, as already reported in the literature for this kind of reaction. The reactions were performed overnight at 80 °C with stoichiometric ratios of 1:2 and 1:10 (Table 1). The reaction progress was evaluated by TLC, and when no significant change could be observed, either by persistence of the starting material or lack of novel spots, the reaction was stopped, and the starting material was recovered. Unfortunately, it was not possible to obtain compound **7** from any of the reported conditions (Table 1, entries I−VI). We reasoned that temperature might have played a role in promoting the condensation reaction, and therefore, high-boiling aprotic polar solvents such as *N*,*N*-dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were investigated to carry out the reaction. We were pleased to notice that when DMF was used as the solvent, no more starting material could be detected by TLC after 3 h despite the fact that the temperature was kept at 80 °C (37% yield; Table 1, entry IX).

Under the same conditions but with DMSO as the solvent, the reaction failed to show any conversion of the starting material to the desired compound (Table 1, entry VII). Therefore, we focused on the use of DMF as the solvent for the condensation reaction. When the stoichiometric amount of urea used was reduced (from 1:10 to 1:2), a longer reaction time, coupled to a decrease in the yield (18%), was observed upon complete consumption of the starting material (Table 1,

entry VIII). Conversely, raising the temperature to 120 °C led to a higher yield (45%) and a reduction of the reaction time to 30 min (Table 1, entry X). We reasoned that the reaction time could be shortened even further by using a microwave reactor, as it is known to reduce the reaction time because of the higher pressure reached in the reaction vessel. Indeed, we were pleased to note that at a 1:10 stoichiometric ratio, the desired 4-(p-tolyl)oxazol-2-amine (**7**) could be obtained in fairly similar yields upon reaction at either 80 °C for 15 min or 120 °C for 3 min (53% and 56% yield, respectively; Table 1, entries XI and XII). Using another high-boiling aprotic polar solvent, N-methylpyrrolidone (NMP), under the same conditions led to similar results (50% and 45% yield, respectively; Table 1, entries XIII and XIV), although the purification of the reaction mixtures with NMP was notoriously more problematic than that with DMF. This led us to consider DMF as the most convenient solvent for the condensation reaction with a stoichiometric ratio of 1:10 in a microwave reactor for 3 min at 120 °C (Table 1, entry XII).
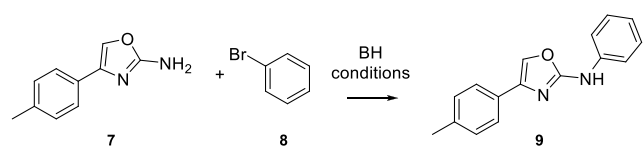
The Buchwald–Hartwig reaction is a cross-coupling reaction of an aryl halide with an amine using a palladium source as the catalyst and a strong base. We decided to take advantage of this well-established synthetic protocol, especially in view of the fact that this procedure has been already applied to many amino heterocycles, including 2-aminooxazoles,[30,31] although this is the first time that this reaction has been used systematically to prepare 4-aryl-substituted 2-aminooxazoles. On the other hand, in the case of 2-aminothiazoles, one palladium-catalyzed reaction has been described that makes use of biaryl phosphorinanes.[32,33] We investigated three different catalytic systems to obtain the title compound **9** from **7** and 4-bromobenzene (**8**) (Table 2): X-Phos Pd G2 and S-Phos Pd G2, which are second-generation Buchwald precatalysts with Pd and the ligand linked together, and DavePhos/Pd(OAc)$_2$. Each of them was used in combination with four bases (tBuONa, Cs$_2$CO$_3$, K$_2$CO$_3$, and K$_3$PO$_4$), and

the reactions were carried out in toluene in a microwave reactor at 130 °C for 10 min, since microwave irradiation has already proven its effectiveness in high-temperature reactions. The DavePhos/Pd(OAc)$_2$ catalytic system in general gave the worst yields (8–11%; Table 2, entries IX–XII), regardless the base used. In the other cases, the conversion of **7** to the desired adduct **9** was appreciable except when K$_2$CO$_3$ was used as the base (Table 2, entries III and VII). This could be due to the fact that this base was too weak to allow the reaction to proceed. However, it must be noticed that in the case of DavePhos/Pd(OAc)$_2$, K$_2$CO$_3$ allowed for the formation of the desired final compound, although in low yield (11%; Table 2, entry XI). With X-Phos Pd G2 or S-Phos Pd G2 as the catalyst, tBuONa gave the best results (Table 2, entries I and V), affording the desired coupling product in 50% and 49% yield, respectively. The use of Cs$_2$CO$_3$ or K$_3$PO$_4$ as the base (Table 2, entries II, IV, VI, and VIII) allowed for the formation of the desired compound in moderate yields (20–42%), although the use of X-Phos Pd G2 provided better overall yields compared with S-Phos Pd G2 (Table 2, entries II and IV vs VI and VIII), whereas in the case of tBuONa the difference was negligible.

The final step was to assess the versatility of the approach. We examined how the BH coupling reaction was affected by the different substitution pattern of the bromobenzene, which was adorned with electron-donating groups (EDGs) or electron-withdrawing groups (EWGs) at different positions (ortho, meta, or para) of the aromatic ring (Scheme 1 and Table 3, reaction B). In this preliminary investigation, the methoxy group was chosen as a representative of the EDGs, whereas the electronegative fluorine atom was the representative of the EWGs. All of the reactions were carried out in a microwave reactor using X-Phos Pd G2 as the catalyst and tBuONa as the base in toluene at 130 °C until consumption of the limiting reagent, which usually occurred in 10 min as shown by TLC. First, it must be noticed that in most cases a substituted bromobenzene was more reactive than the unsubstituted counterpart. Although it cannot be a general rule of thumb, in our case an EDG such as the methoxy group resulted in better yields (**27–29**, 48–71% yield) than an EWG such as fluorine (**24–26**, 37–59% yield). In both cases, ortho substitution led to the best results, whereas at this point it would be too speculative to establish whether the meta or para position is detrimental to the yield (Table 3). In a similar way, we wanted to evaluate whether the condensation with urea using the conditions described above could be applied to several substituted acetophenones (**10–16**) (Scheme 1 and Table 3, reaction A). For this preliminary evaluation, we used acetophenones substituted at the ortho, meta, or para position with EDGs and EWGs. As expected, the effect of the substituent is negligible (Table 3), and the yield for this reaction was always around 50%. Once the versatility of the procedure was demonstrated, we applied it to the synthesis of 2-aminooxazoles **30**, **31**, **34**, and **36** (Scheme 2), which are structurally related to 2-aminothiazoles **1–4**,[7,10] respectively. These derivatives were successfully synthesized following the procedure reported above, further confirming its versatility. It should also be noted that in these cases the standard Hantzsch protocol with substituted ureas did not lead to the title compounds even though the reaction was performed under different conditions (data not shown).

The final step of this research was to evaluate both the actual isomerism and bioisosterism of the 2-aminooxazoles compared with the corresponding 2-aminothiazoles. First, the synthesized

Table 2. Optimization of the Buchwald–Hartwig Reaction Conditions^a

entry	Pd source	base	yield (%)
I	X-Phos Pd G2	t-BuONa	50
II	X-Phos Pd G2	Cs$_2$CO$_3$	42
III	X-Phos Pd G2	K$_2$CO$_3$	0
IV	X-Phos Pd G2	K$_3$PO$_4$	37
V	S-Phos Pd G2	t-BuONa	49
VI	S-Phos Pd G2	Cs$_2$CO$_3$	20
VII	S-Phos Pd G2	K$_2$CO$_3$	0
VIII	S-Phos Pd G2	K$_3$PO$_4$	28
IX	Dave Phos/Pd(OAc)$_2$	t-BuONa	8
X	Dave Phos/Pd(OAc)$_2$	Cs$_2$CO$_3$	8
XI	Dave Phos/Pd(OAc)$_2$	K$_2$CO$_3$	11
XII	Dave Phos/Pd(OAc)$_2$	K$_3$PO$_4$	11

^{a}Reaction conditions: **7** (1 equiv), **8** (0.5 equiv), base (1 equiv), catalyst (0.1 equiv), toluene (2.5 mL/mmol), t-BuOH (0.5 mL/ mmol), 130 °C, 10 min, MW. See the Supporting Information for details.

Scheme 1[a,b]
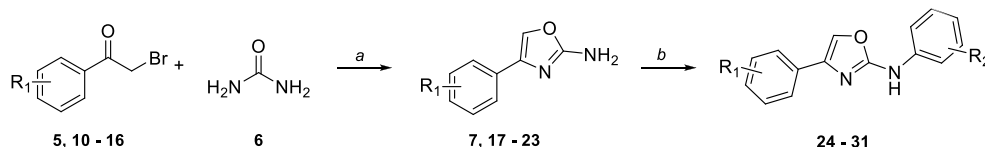
[a]Reagents and conditions: (a) DMF, MW (120 °C, 300 W), 3 min, 25−57%; (b) aryl bromide, tBuONa, X-Phos Pd G2, tBuOH, toluene, MW (130 °C, 300 W), 15 min, 10−71%. [b]For complete structures, see Table 3.

### Table 3. Synthesis of Variously Substituted 2-Aminooxazoles

Entry	R_1	Yield passage A (%)
5, 7	p-CH$_3$	56
10, 17	o-CH$_3$	52
11, 18	m-CH$_3$	52
12, 19	o-Br	40
13, 20	m-Br	57
14, 21	p-F	41
15, 22	2-F, 5-CF$_3$	25
16, 23	p-OCH$_3$	38
33		49

Entry	R_1	R_2	Yield passage B (%)
24	p-CH$_3$	o-F	59
25	p-CH$_3$	m-F	37
26	p-CH$_3$	p-F	53
27	p-CH$_3$	o-OCH$_3$	71
28	p-CH$_3$	m-OCH$_3$	59
29	p-CH$_3$	p-OCH$_3$	48
30	2-F, 5-CF$_3$	p-CH$_3$	31
31	p-OCH$_3$	p-CH$_3$	10
34			16

compounds were evaluated for their effect toward *Mtb*, and we were pleased to note that compounds **30**, **34**, and **36** bearing a 2-aminooxazole moiety showed promising activity toward *Mtb*, with a trend similar to that of 2-aminothiazoles **1**−**4**. Indeed, as in the case of 2-aminothiazoles, it is possible to appreciate that isoxazole derivatives **34** and **36** were generally more active than the aryl analogues, with negligible cytotoxicity toward VERO cells (data not shown).

Afterward, as the final proof of the isosterism of the novel molecules, we evaluated other physicochemical and in vitro ADME properties, such as (*i*) the kinetic solubility in water and phosphate-buffered saline (PBS) at pH 7.4, (*ii*) the metabolic stability in human liver microsomes (HLM), and (*iii*) the reactivity toward glutathione (GSH). In particular, the last of these was considered important in order to evaluate the tendency of these compounds to be PAINS.

Kinetic Solubility Measurements. The kinetic solubilities of selected 2-aminothiazoles were assessed starting from DMSO stock solutions of **1**−**4** and compared to those of the corresponding isosteres, 2-aminooxazoles **30**, **31**, **34**, and **36**. This approach was preferred to the measurement of equilibrium solubility starting from powder because the latter is significantly influenced by the nature of the solid state (amorphous vs crystalline, polymorphic forms), which generally is not thoroughly investigated at the discovery stage.[34] In Table 4, the values of the kinetic solubilities in water and pH 7.4 PBS (expressed in μM) are reported. In general, kinetic solubility values in water ranged from 0.7 μM (log S = −6.15) for the least soluble **31** to 55 μM (log S = −4.26) for the most soluble **3**, spanning 2 orders of magnitude, while in PBS buffer at physiological pH they were between 1.1 μM (log S = −5.95) for **31** and 27.7 μM (log S = −4.56) for **3**. The two scales of log S values in water and PBS were positively correlated (log S_{water} = (1.40 ± 0.18) log S_{PBS} + (2.26 ± 0.96); n = 7; r^2 = 0.921; s = 0.19; F = 59), with the sole exclusion of

Scheme 2[a]
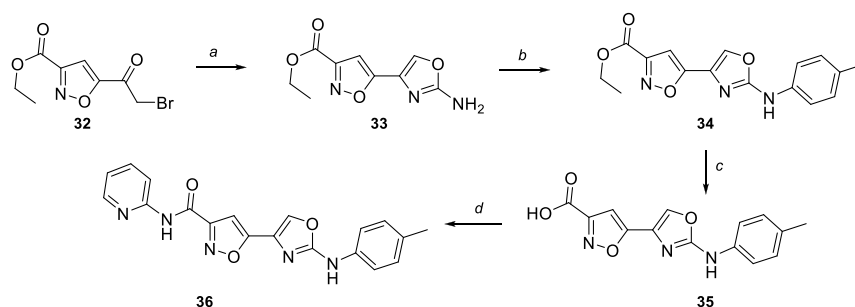
[a]Reagents and conditions: (a) urea, DMF, MW (120 °C, 300 W), 3 min, 49%; (b) 4-bromotoluene, tBuONa, X-Phos Pd G2, t-BuOH, toluene, MW (130 °C, 300 W), 15 min, 16%; (c) LiOH, THF/H$_2$O/MeOH 3:1:1, rt, 3 h, quantitative; (d) 2-aminopyridine, TBTU, EDC, TEA, anhydrous DMF, rt, 5 h, 57%.

Table 4. Biological and Physicochemical Evaluation of 2-Aminothiazoles and 2-Aminooxazoles

compd	MIC (μM)	kinetic solubility (μM) water	kinetic solubility (μM) PBS pH 7.4	HLM $t_{1/2}$ (min)[d]	HLM Cl'$_{int}$ (mL min^{-1} kg^{-1})[e]	mean GSH conjugate area	GSH conjugate area ratio (%)
1	27.5[a]	24 ± 2.7	7.5 ± 1.1	22.4 ± 1.6	27.9	303	10.4 ± 1.7
2	13[a]	20 ± 2.4	1.2 ± 0.2	14.5 ± 0.5	42.9	616	13.9 ± 0.2
3	1.5[b]	54.9 ± 15	27.7 ± 8	3.3 ± 0.3	188.8	34	3.7 ± 0.5
4	0.16[b]	2.9 ± 0.5	2.4 ± 0.5	16.1 ± 0.2	38.8	111	7.1 ± 0.9
30	12.3[a]	5.2 ± 0.6	5.9 ± 0.5	22.6 ± 1.2	27.6	2117	14.2 ± 5
31	>100[a]	0.7 ± 0.2	1.1 ± 0.3	20.9 ± 1.4	29.9	467	14.2 ± 1.5
34	2.3[a]	9.1 ± 2	6.8 ± 1.1	2.7 ± 0.8	226.1	120	15.8 ± 1.3
36	6.9[c]	24 ± 4	9.3 ± 1.2	15 ± 0.1	41.5	82	2.1 ± 0.9

[a]MIC values determined by MABA are means of replicate experiments (SD < 15%).[10] [b]MIC determined by microdilution.[7] [c]Minimun Inhibitory Concentration, determined by REMA method. [d]Measured in human liver microsomes and expressed in minutes. [e]Intrinsic clearance was calculated as (0.693/in vitro $\tau_{1/2}$) × (mL of incubation/mg of microsomes) × (45 mg of microsomes/g of liver) × (20 g of liver/kg of body weight).

2-aminothiazole **2**, for which the solubility in PBS was −1.2 log unit lower than that in water. Comparing the 2-aminothiazole/2-aminooxazole isosteric couples **1/31**, **2/30**, **3/34**, and **4/36**, we did not observe any significant difference between the average solubility values measured either in water [average log S (2-aminothiazoles) = −4.78 ± 0.54, mean ± SD (n = 4); average log S (2-aminooxazoles) = −5.27 ± 0.54, mean ± SD (n = 4); p > 0.05] or in PBS buffer [mean log S (2-aminothiazoles) = −5.30 ± 0.59, mean log S (2-aminooxazoles) = −5.34 ± 0.41; p > 0.05]. The compounds that showed the two best rankings in kinetic solubility values were the already cited 2-aminothiazole **3** (55 μM, equal to 18 μg/mL, in water; 27 μM, equal to 9 μg/mL, in PBS) and 2-aminooxazole **36** (24 μM, equal to 8.7 μg/mL, in water; 9.3 μM, equal to 3.4 μg/mL, in PBS).

Metabolic Stability in Human Liver Microsomes. We next determined the metabolic stabilities of the set of 2-aminothiazoles and 2-aminooxazoles in human liver microsomes (HLM). Although liver microsomes are the simplest in vitro model for phase I metabolism, a first assessment of metabolic stability by this subcellular model is useful since compounds presenting short in vitro half-lives ($t_{1/2}$) in this assay are those most likely to encounter later in vivo pharmacokinetic issues (i.e., high in vivo clearance and, as a consequence, reduced oral bioavailability).[35] An "intrinsic clearance" (Cl'$_{int}$) can also be calculated from the in vitro microsomal stability data (Table 4). As can be seen from Table 4, two compounds of the set (i.e., the two ethyl esters **3** and **34**) were characterized by the shortest half-lives in HLM (i.e., $t_{1/2}$ = 3.9 min for **3** and 2.7 min for **34**) because of their rapid cleavage to give the corresponding acids. Indeed, the corresponding acids showed a reduced clearance in comparison to the esters (Cl'$_{int}$ = 160.7 mL min^{-1} kg^{-1} for ester **3** and 226.1 mL min^{-1} kg^{-1} for ester **34** compared with Cl'$_{int}$ ≈ 37 ± 1 mL min^{-1} kg^{-1} for the corresponding acids). For all of the remaining compounds, we could not see a clear dependence of the metabolic stability on the substitution of the core 2-aminothiazole ring with the isostere 2-aminooxazole. Indeed, even though 2-aminooxazole **30** had a significantly longer half-life than the corresponding 2-aminothiazole **2** ($t_{1/2}$ = 22.6 ± 1.2 min vs 14.5 ± 0.5 min, mean ± SD (n = 3); p < 0.01), for the other two isostere couples **31/1** and **36/4** the half-lives were comparable, suggesting that the preferred metabolic pathways in HLM of compounds **1** and **4** did not involve the sulfur atom of the thiazole core ring.

Reactivity of Selected 2-Aminothiazoles and 2-Aminooxazoles with GSH. Compounds defined as PAINS generally give false-positive results in high-throughput screening assays, as they tend to react nonspecifically. Thus, an investigation of the reactivities of the set of 2-aminothiazoles and the corresponding 2-aminooxazoles was carried out. Test compounds were incubated with GSH, the most abundant thiol in cells, for 24 h before analysis for the formation of the GSH conjugates by HPLC−MS/MS. In full-scan MS analysis only the molecular ion [M + H]$^+$ was observed for all of the compounds tested, while for the GSH conjugates the presence of both the singly charged ion ([M + H]$^+$ conjugate) and the doubly charged ion ([M + 2H]$^{2+}$ conjugate) were detected (e.g., Figure S1). The percentage ratios of the GSH conjugate formed were calculated as (peak area of [M + H]$^+$ conjugate + peak area of [M + 2H]$^{2+}$ conjugate)/(peak area of [M + H]$^+$ compound), and the results are reported in Table 4. In general, at 24 h, despite the fact that GSH had been employed in a large molar excess (1:100), only a small percentage of the starting compounds reacted with GSH. In fact, the percentages of compound−GSH conjugates ranged from 2.1% for **36** to 16% for **34**. Given the overall poor reactivity of these compounds toward GSH, it could be deduced that they do not act like PAINS, and thus, their activity can be considered the result of a specific interaction with a molecular target.

Conclusion. We have investigated the possibility of exploiting the 2-aminooxazole scaffold as a novel privileged structure in medicinal chemistry. Whereas the 2-aminothiazole scaffold is widely used in many bioactive molecules, either in the early drug discovery phases or in the market, the 2-aminooxazole scaffold, an isostere of 2-aminothiazole, has been poorly investigated. We first set up a synthetic protocol for the preparation of N,4-disubstituted 2-aminooxazoles and then evaluated a small set of 2-aminooxazoles and the corresponding 2-aminothiazoles with regard to their biological and pharmacokinetic characteristics. We noticed that the antitubercular activity is maintained in the 2-aminooxazole derivatives, with a trend similar to that of the 2-aminothiazoles, confirming how the two nuclei can be considered bioisosteres. Moreover, the 2-aminooxazole structure does not negatively affect other physicochemical or in vitro PK parameters such as solubility, metabolic stability, and unselective reactivity with thiols. A larger set of molecules and assays are needed to confirm this and are currently under investigation in our laboratories.

■ ASSOCIATED CONTENT

ⓈⒾ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsmedchemlett.0c00173.

Description of the chemical and biological methods, evaluation of MICs, and analytical data related to the synthesized compounds (PDF)

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E.A., G.A., M.G., M.L.P.: synthesis, data collection, and data analysis. M.R.P. and G.M.: MIC determination and manuscript revision. F.V.: studies of solubility and microsomal stability and manuscript revision; G.C.: resources, supervision, and manuscript revision. M.P.: study design, supervision, and manuscript writing and revision.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

ADME, absorption, distribution, metabolism, and excretion; DMF, *N,N*-dimethylformamide; DMSO, dimethyl sulfoxide; EDC, *N*-(3-(dimethylamino)propyl)-*N′*-ethylcarbodiimide; EDG, electron-donating group; EWG, electron-withdrawing group; HLM, human liver microsomes; GSH, glutathione; MDR, multidrug-resistant; *Mtb*, *Mycobacterium tuberculosis*; MW, microwave; PAINS, pan-assay interfering compounds; SAR, structure−activity relationship; TB, tuberculosis; TBTU, *O*-(benzotriazol-1-yl)-N,N,N′,N′-tetramethyluronium tetrafluoroborate; TDR, totally drug-resistant; TEA, triethylamine; THF, tetrahydrofuran; TLC, thin-layer chromatography; XDR, extensively drug-resistant.

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