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N-(acridin-9-yl)arenesulfonamides: Synthesis, quantum chemical studies and crystal structure analysis to establish the tautomeric preferences

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ABSTRACT

The potentiality of the N-(acridin-9-yl)arenesulfonamide moiety as a hybrid pharmacophore due to the distinct pharmacological activities of acridines and aryl/heteroaryl sulfonamides prompts to synthesise N-(acridin-9-yl)arenesulfonamides and study their structural properties. Various N-(acridin-9-yl)arene/heteroarenesulfonamides were obtained through the development of a new methodology adopting the $Pd_2(dba)_3$-catalyzed C–N bond formation strategy for the reaction of 9-chloloroacridine with arene/heteroarenesulfonamides. The 1H and ^{13}C NMR spectra suggest these N-(acridin-9-yl)arene/heteroarenesulfonamides to exist solely as the sulfonimide tautomer rather than anticipated sulfonamide form and was confirmed by the single crystal XRD analysis of one of the newly synthesized compounds. The quantum chemical studies rationalized this tautomeric preference revealing that the sulfonimide tautomers are more stable than the sulfonamide tautomers by −0.67 to −5.12 kcal/mol in the gas phase. In the solid state, the sulfonimide tautomer is stabilized by intermolecular hydrogen bond between N–H···O–S and π– π stacking between the acridine rings.

1. Introduction

The acridine moiety exerts its anticancer activity by intercalating between base pairs of double-stranded DNA through π-π interactions[1,2] and represents the essential pharmacophoric feature of drugs such as amsacrine (anticancer),[3] mepacrine (antimalarial),[4] proflavin (topical antiseptic, antibacterial)[5] (Fig. 1A). On the other hand, sulfonamides have long been the subject of pharmaceutical interest due to their diverse biological activities[6] and solid state structural properties (originating from polymorphism and tautomerism).[7,8] The sulfonamide group contributes to the pharmacophoric features in many drugs including the recently approved bosentan (antihypertensive),[9] sulfasalazine (antibacterial),[10] sulfadiazine (antibacterial),[11] sulfathiazole (antibacterial),[12] sulfamethoxazole (antibacterial),[13] sulfamethazine[14] (Fig. 1B).

Many hybrid sulfonamides with different heterocycles have gained attention for the development of drugs/leads. The recent examples include (i) chloroquinoxaline sulfonamide (NSC-339004)[15,16] is a synthetic heterocyclic sulfonamide which has been identified as investigational drug for the treatment of cancer, is in the clinical trial stage.

Chloroquinoxaline was tested and found to be both a topoisomerase-IIa and a topoisomerase-IIb poison; (ii) BMS-193884[17] which contain isoxazole sulfonamide moeity was identified as endothelin receptor antagonist, (iii) AM-0466[18] and PF-050897771[19] are clinical candidate with selective sodium channel (Nav1.7) inhibitory activity for the management of pain; (iv) a quinazoline sulfonamide derivative[20] has been reported as anticancer agent. (Fig. 2A). All these examples represent the hybrid sulfonamides with different heterocycles. Considering the importance of these two moieties (acridine and sulfonamide) in medicinal chemistry, *N*-(acridine-9-yl)arenesulfonimide (NAAS) can also

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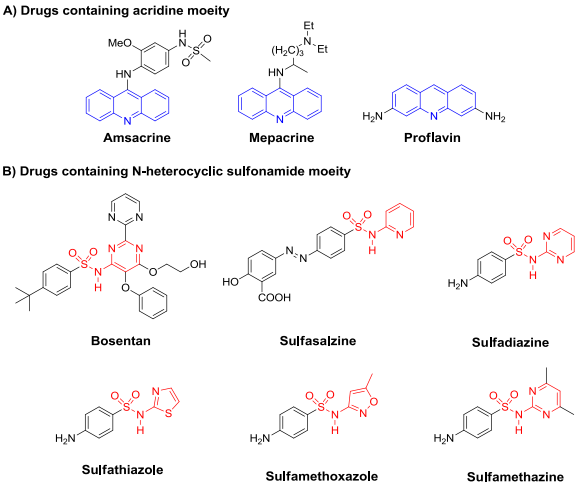


Fig. 1. A) Representative drugs containing the acridine moeity; B) Drugs containing N-heterocyclic sulfonamide moieties.

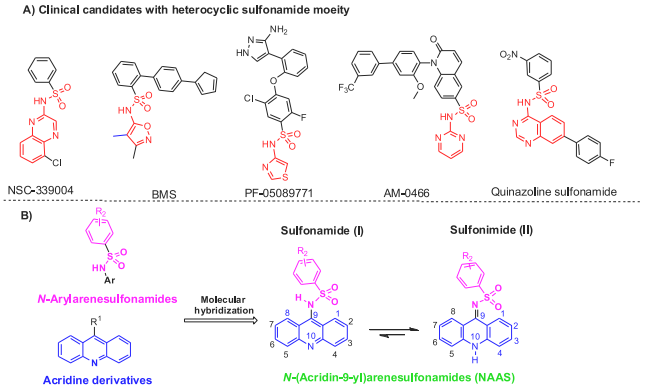


Fig. 2. A) Clinical sulfonamide candidates with different heterocycles; B) NAAS considered in present study representing a hybrid pharmacophore of sulfonamide and acridine moeity. The equilibrium represents the possible sulfonamide-sulfonimide tautomers of NAAS.

be considered as novel hybrid pharmacophore (Fig. 2B).

It is surprising to note that hybrid of sulfonamide and acridine heterocycle as a pharmacophore was not explored till now, the reason could be the non availability of method of its synthesis or difficulty in synthesis of this class of compound. Thus, herein, we report, the synthesis of NAAS through the development of palladium catalyzed method. The quantum chemical studies were carried out to rationalize the formation of sulfonimide tautomer as the sole product, and finally the crystal structure analysis was carried out to confirm the tautomeric preferences.

Tautomerism in drugs is a topic of contemporary interest due to its importance in medicinal chemistry,[21–24] computer-aided drug design,[25–28] drug delivery,[29] drug discovery,[30] understanding the interactions of the drug molecules with the biological targets[31,32] chemical reactivity,[33] structural property[34] and polymorphism.[35] Our lab has been extensively working on the importance of pharmacophoric feature vs tautomer of medicinally important compounds.[23,36–40] Continuing the effort, it was realized that NAAS can represent a pharmacophore and can exhibit tautomeric preference towards sulfonimide tautomer, the results are presented below.

2. Results and discussion

2.1. Synthesis

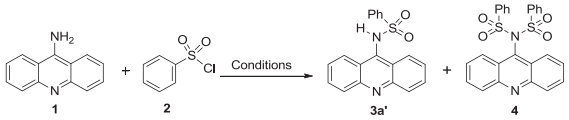
Due to the lack of information on the synthesis of such class of molecules,[41] initially, we adopted S–N bond formation strategy for the synthesis of *N*-(acridin-9-yl)benzenesulfonamide **3a′** from the reaction of 9-aminoacridine (**1**) and benzenesulfonyl chloride (**2**) using literature reports (Table 1).[42–48] The treatment of 9-aminoacridine (**1**) with benzenesulfonyl chloride (**2**) under various conditions either did not form *N*-(acridin-9-yl)benzenesulfonamide **3a′** (Table 1, entry 1–8) or led to the formation of the bissulfonylated product **4** in poor yield (Table 1, entry 9).

Next, we adopted the C–N bond formation strategy involving the aromatic nucleophilic substitution reaction of 9-chloroacridine (**5**) with arenesulfonamide (**6**) to from *N*-(acridin-9-yl)arenesulfonamides (**3a′**, Table 2).

The reaction of 9-chloroacridine with arenesulfonamide in the absence of transition metal catalyst gave poor yield of desired product (entry 1–3, Table 2). We observed that the aromatic nucleophilic substitution reaction of heteroarylhalides with arenesulfonamide has been reported under the influence of Cu(I)[49,50] and Pd(II)[51,52] derived catalysts in the presence of suitable ligand and stoichiometric amounts of base but till date there is no report on the reaction of **5** with **6** to form **3′**. Thus, we used the reaction conditions of these literature reports[49–52] for the model reaction of **5** with benzenesulfonamide **6a** so as to find the best operative reaction condition to form **3a′** under the influence of either CuI or $Pd_2(dba)_3$ as the transition metal derived catalysts (TM-Cat) as well as different variation of the reaction conditions such as the use of different ligand, base, and solvent at 80–100 °C (oil bath) for 12 h (Table 2).

The Cu(I)-catalyzed reactions led to either no product formation or produced **3a** in poor yields (GC-MS; ESI) (Table 2, entries 4–10). Amongst the various trials for the $Pd_2(dba)_3$ catalyzed reaction (Table 2, entries 11–16), the best result was obtained in performing the reaction in ^{t}BuOH (Table 2, entry 14) affording **3a** in 56% yield. With this optimized condition in hand, we performed the reaction of **5** with different arenesulfonamides **6** to obtain the *N*-(acridin-9-yl)arenesulfonamides (**3a**-**3o**) in 55–60% yields (Table 3).

Table 1
Synthesis of *N*-(acridin-9-yl)benzenesulfonamide by conventional methods.



Entry	Reaction conditions	Yield (%)		Literature reports
		3a[a]	**4**	
1	MeCN, Pyridine, rt, 12 h	trace	0	Ref.42
2	Pyridine, 100 °C, 12 h	trace	0	Ref.43
3	H_2O, Na_2CO_3, 80 °C, 12 h	0	trace	Ref.44,4544,4544,45
4	Silica gel, rt, 12 h	0	0	Ref.46
5	EtOH/AcOH, reflux, 12 h	0	0	Ref.47
6	Water, Na_2CO_3, pH = 8, rt, 12 h	0	0	Ref.48
7	MeCN, Na_2CO_3, reflux, 12 h	0	0	Current work
8	MeCN, reflux, 12 h	<5	0	Current work
9	MeCN, K_2CO_3, reflux, 12 h	0	15	Current work

[a] **3a** is the energetically stable sulfonimide tautomer of **3a′** and found to present under experimental condition (*vide infra*).