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Synthesis and antimicrobial evaluation of guanylsulfonamides

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Abstract—A series of guanylsulfonamides, 2-amino-9-[2-substituted-4-(4-substituted piperidin-1-sulfonyl)phenyl]-1,9-dihydropurin-6-ones, was synthesized by adopting reductive aminoformylation of 2-amino-5-nitro-6-[4-(piperidin-1-sulfonyl)phenylamino]-*3H*-pyrimidin- 4-one and subsequent intramolecular ring condensation as key steps. All the guanylsulfonamides were assayed for their in vitro antibacterial activities against *Klebsiella pneumoniae*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus*, and *Streptococcus faecalis*, and their antifungal activities against *Aspergillus flavus*, *Aspergillus niger*, and *Candida albicans*. Of the guanylsulfonamides, **13e** and **13f** displayed better antibacterial activities than that of Norfloxacin against the bacterial strains *S. aureus* and *S. faecalis* except **13f** against *S. faecalis*, which exhibited the activity similar to that of Norfloxacin. Against the fungal strains *A. flavus* and *A. niger*, **13g** and **13h** showed similar activities to that of Griseoflavin-16 except **13h** against *A. niger*, which displayed a profound drop in the activity compared to that of Griseoflavin-16. The remarkable inhibition of the growth of the bacterial and fungal strains makes these substances promising microbial agents.

In recent decades, microbial diseases are more prevalent than they were during the first half of the last century and are still difficult to be diagnosed clinically. To combat them, various synthetic and semi-synthetic antimicrobial drugs have been used in clinical practice.[1,2] In spite of many significant developments in the antimicrobial therapy, many problems remain to be solved for most of the antimicrobial drugs available. Hence, discovery of novel antimicrobial agents with better pharmacological profile is still highly desirable.

Sulfonamides are among the most widely used antibacterial agents in the world, chiefly because of their low cost, low toxicity, and good activity against common bacterial diseases. The synergetic action of sulfonamides with Trimethoprim has brought about enormous resurgence of sulfonamide usage everywhere over the last decade. However, the most common side effects of this class of drugs are nausea, vomiting, diarrhea, anorexia, and hypersensitivity reaction.[3] Piperazine sulfonamides exhibit diverse pharmacological activity such as MMP-3 inhibition, antibacterial activity, and Carbonic anhydrase inhibition.[4]

On the other hand, 9-substituted purine derivatives possess broad pharmacological activity. For example, acyclovir,[5] and ganciclovir,[6] are active against viral diseases caused by HSV-1, HSV-2, VZV, and the human CMV[7] while 9-benzylpurine derivative, 2-chloro-6-(2-furyl)-9-(4-methoxyphenylmethyl)-*9H*-purine, and 9-sulfonylated/sulfenylated-6-mercaptopurine derivatives are active against bacterial diseases caused by *Mycobacterium tuberculosis*.[8] Also, 9-aryl-2,6-diaminopurines and 2-amino-9-methyl-6-purinethiol show antitumor activity.[9] Furthermore, several 9-phenylguanine derivatives are found to be good irreversible inhibitors of Guanosine deaminase[10] and Xanthine oxidase.[11] Having these observations in mind, we designed and synthesized a series of novel heterocyclic chemical entities, guanylsulfonamides, possessing bioactive guanine and sulfonamide scaffolds and evaluated their antimicrobial activities against various bacterial and fungal strains.

For the construction of the target guanylsulfonamides, a retrosynthetic approach was designed based on intramolecular ring closure of arylamino pyrimidines (see Chart 1) and is furnished in Chart 2. The intramolecular ring closure precursor **12** was envisioned to derive from **11** since a disconnection of the bond between C-8 and N-9 on the target molecule, guanylsulfonamide gives a synthon, **A** of the intramolecular ring closure precursor **12** and a disconnection of the imine bond of the synthon **A** provides a synthetic equivalent for the pre precursor **11**. The compound **11** could be derived from **6** and **10**

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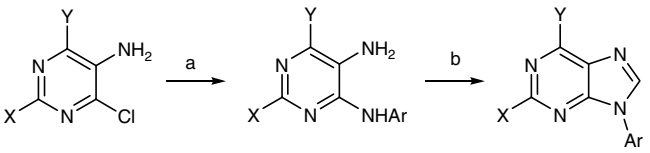


Chart 1. (a) Ar–NH_2; (b) $CH(OEt)_3$, H^+.

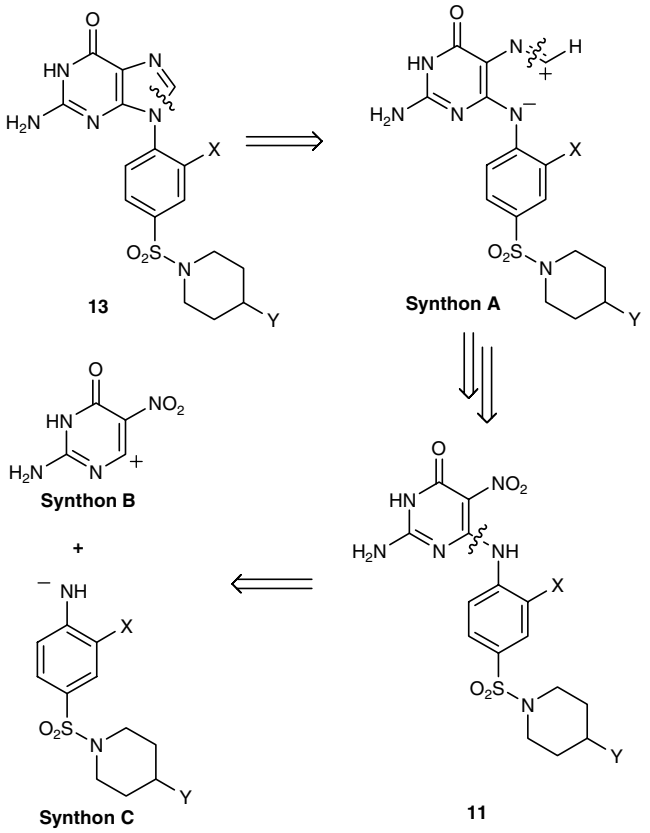
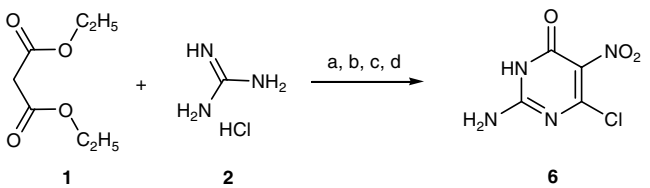


Chart 2.

as its retrosynthetic analysis produces synthon **B** and synthon **C**.

The compound **6**, 2-amino-6-chloro-5-nitro-*3H*-pyrimidin-4-one, was synthesized by adopting the methods given in the literature (Scheme 1).[12–14]

When pyrimidinone, 2-amino-6-hydroxy-*3H*-pyrimidin-4-one (**3**), obtained by the condensation of guanidine with malonic acid diethylester was treated with $POCl_3$, 4,6-dichloropyrimidin-2-ylamine (**4**) was formed.



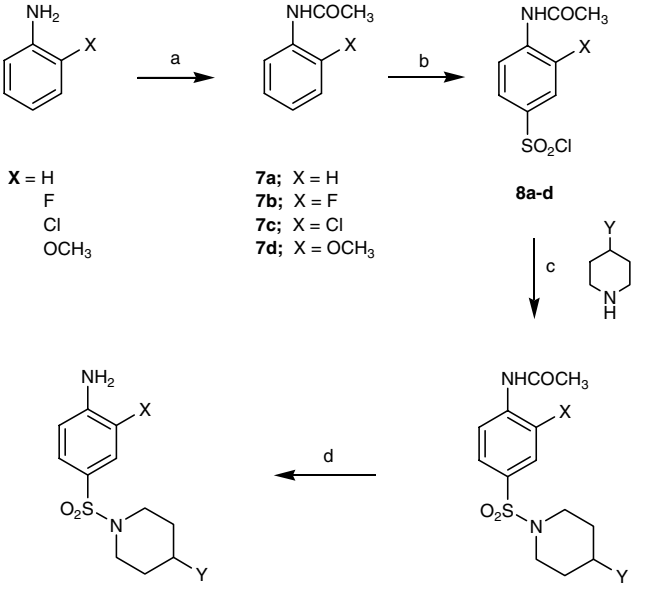
Scheme 1. Reagents: (a) MeOH, NaOMe; (b) $POCl_3$, Et_3N; (c) 1 N NaOH, H_2O; (d) HNO_3, H_2SO_4.

Hydrolysis of **4** using strong NaOH followed by nitration provided 2-amino-6-chloro-*3H*-pyrimidin-4-one (**5**) and **6**, respectively.

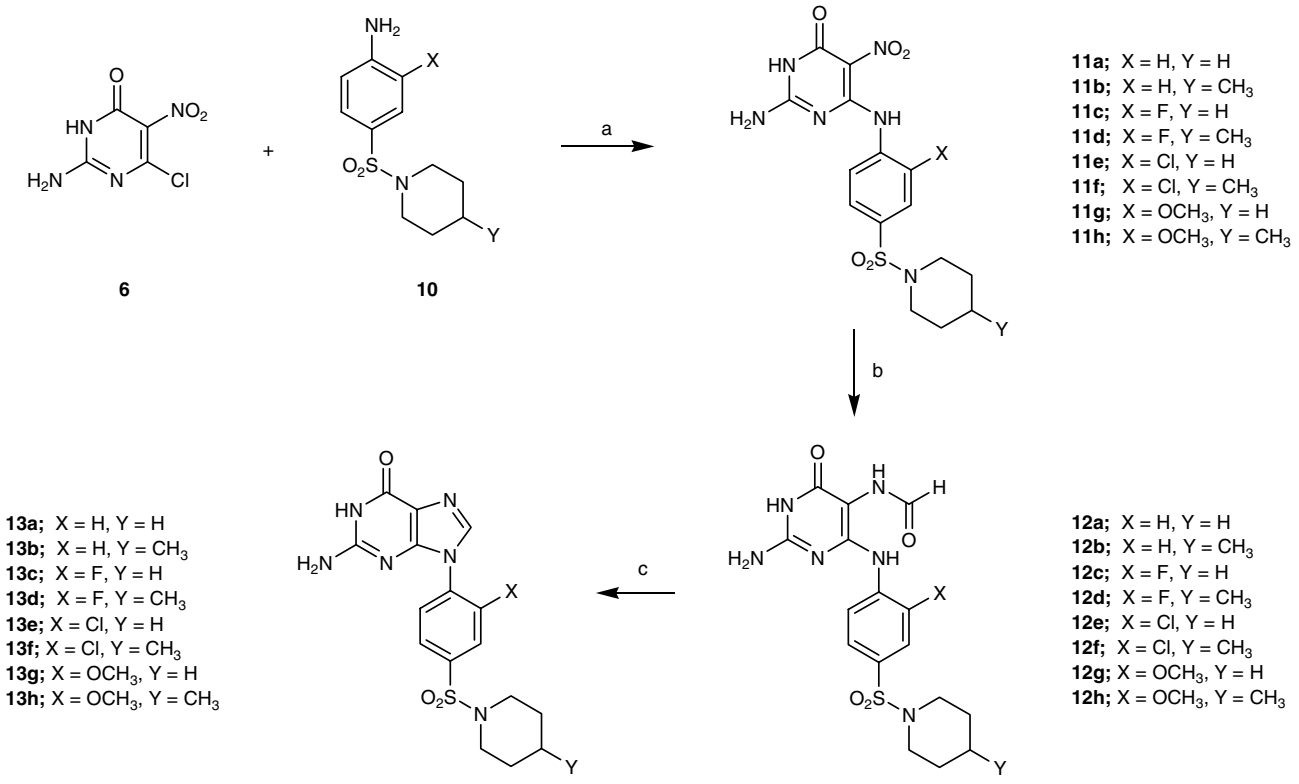
On the other hand, an equivalent synthon **C**, 2-substituted-4-(4-substituted piperidin-1-sulfonyl)phenylamine derivatives (**10a**–**10h**), was synthesized by adopting a four-stage synthetic strategy as shown in Scheme 2. Compound **8a**, synthesized from aniline using acetylation[15] followed by chlorosulfonylation methods,[16] was subjected to substitution followed by hydrolysis reactions to afford **9a** and **10a**, respectively. In a similar manner, **10b**–**10h** were synthesized.

Eventually, guanylsulfonamide analogues (**13a**–**13h**) were synthesized by adopting a three-step strategy as depicted in Scheme 3. When **11a**, obtained by the substitution of **6** with **10a**, was submitted to reductive aminoformylation and subsequent intramolecular ring closure reactions, guanylsulfonamide **13a** resulted as a sole product. Analogues **13b**–**13h** were synthesized akin to the method used for **13a**.

All the guanylsulfonamides **13a**–**13h** were assayed for their in vitro antibacterial activity against a panel of pathogenic bacterial strains such as *Klebsiella pneumoniae* (ATCC-13883), *Escherichia coli* (ATCC-25922), *Pseudomonas aeruginosa* (ATCC-27853), *Bacillus subtilis* (ATCC-6033), *Staphylococcus aureus* (ATCC-25923), and *Streptococcus faecalis* (ATCC-29212). The assays were carried out using twofold serial dilution technique.



Scheme 2. Reagents: (a) $(CH_3CO)_2O$, H_2O; (b) $ClSO_3H$; (c) MeOH; (d) HCl, MeOH.



Scheme 3. Reagents: (a) MeOH, Et_3N; (b) Zn, HCOOH; (c) H^+, $HOCH_2$ CH_2OH.

Dimethyl sulfoxide and one of the potent antibacterial drugs Norfloxacin, an oral broad-spectrum fluoroquinolone antibacterial agent used for the treatment of urinary tract infections, were used as solvent control and standard, respectively. The results are furnished in Table 1.

Among the guanylsulfonamide analogues, **13a** and **13b** having no substituents on the 2-position of the –Ph and the 4-position of the piperidine ring were inactive at the maximum concentration (64 μg mL^{-1}) against *K. pneumoniae*, *E. coli*, and *B. subtilis* except **13b** against *B. subtilis*. However, these compounds (**13a** and **13b**) showed activity against *P. aeruginosa*, *S. aureus*, and *S. faecalis* at the maximum concentration. When a $–CH_3$ was introduced at the 4-position of the piperidine ring, there were no profound loss or gain in the activities observed against *P. aeruginosa*, *S. aureus*, and *S. faecalis*.

Against all the organisms except *P. aeruginosa*, **13c** with a –F on the 2-position of the –Ph exhibited enhanced activity compared to its unsubstituted analogue **13a**. Introduction of a $–CH_3$ on the 4-position of the piperidine ring of **13c**, thereby producing analogue **13d**, did not alter the activity against *K. pneumoniae*, *P. aeruginosa*, and *S. aureus*. However, due to the $–CH_3$ introduction, an increase in the activity, about twofold, against *E. coli* as well as a decrease in the activity, about twofold, against *B. subtilis* and *S. faecalis* were observed.

When the –F was substituted by a –Cl in **13c**, thereby producing analogue **13e**, a remarkable enhancement in the activity was observed against *S. aureus* and *S. faecalis*. Due to the –Cl, the growths of *S. aureus* and *S. faecalis* were inhibited at a minimum concentration of 4 μg mL^{-1}. An appreciable enhancement in the activities of **13e** was noticed against rest of the organisms as well. The guanylsulfonamide **13f** with a $–CH_3$ at the 4-position of the

Table 1. Antibacterial activities of 2-amino-9-[2-substituted-4-(4-substituted piperidin-1-sulfonyl)phenyl]-1,9-dihydropurin-6-ones (**13a**–**13h**)

Compound	X	Y	MIC, μg mL^{-1}					
			K. pneumoniae	*E. coli*	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*S. faecalis*
13a	H	H	—	—	64	—	64	64
13b	H	CH_3	—	—	64	64	64	64
13c	F	H	32	64	64	32	32	16
13d	F	CH_3	32	32	64	64	32	32
13e	Cl	H	16	16	8	32	4	4
13f	Cl	CH_3	16	16	16	32	4	8
13g	OCH_3	H	32	32	64	16	64	64
13h	OCH_3	CH_3	32	16	64	16	32	32
Norfloxacin			16	16	8	32	8	8

piperidine ring and a –Cl on –Ph has similar activity as **13e** against all the organisms except *P. aeruginosa* and *S. faecalis*. Against these two organisms, the $-CH_3$ replacement caused a profound drop in the activity to levels lower than that of **13e**.

On the other hand, substitution of a $-OCH_3$ in place of the –Cl in **13e** remarkably decreased the activity against all the organisms except *B. subtilis*. Against *B. subtilis*, the $-OCH_3$ substitution noticeably enhanced the activity displayed by the –Cl substituted analogue **13e**. When a $-CH_3$ was introduced at the 4-position of the piperidine moiety in **13g**, an increase in the activity was observed against *E. coli*, *S. aureus*, and *S. faecalis* whereas there was no appreciable difference in the activity noticed against *K. pneumoniae*, *P. aeruginosa*, and *B. subtilis*.

The antifungal activity of the guanylsulfonamides **13a**–**13h** on a panel of pathogenic fungal strains such as *Aspergillus flavus* (NCIM-539), *Aspergillus niger* (NCIM-590), and *Candida albicans* (NCIM-C27) was evaluated using twofold serial dilution method. Dimethyl sulfoxide and Griseoflavin-16, an antifungal drug commonly used to cure fungal infection affecting the skin, hair, and nail known as ringworm, were used as solvent control and standard, respectively. The results are presented in Table 2.

Of the guanylsulfonamides **13a**–**13h**, **13a** did not show activity against all the fungal strains at the maximum concentration (64 $\mu g\,mL^{-1}$). In **13a**, a $-CH_3$ substitution at the 4-position of the piperidine ring (**13b**) or a –F substitution at the 2-position of the –Ph (**13c**) also did not exhibit activity at the maximum concentration against all the fungal strains. However, **13d** having $-CH_3$ on the 4-position of the piperidine ring and –F on the 2-position of the –Ph displayed activity at 64 $\mu g\,mL^{-1}$ against *A. flavus* and *C. albicans* and at 32 $\mu g\,mL^{-1}$ against *A. niger*.

Introduction of a –Cl instead of the –F on the 2-position of the –Ph in **13c** (resulting in analogue **13d**) exhibited activity at the maximum concentration against all the fungal strains. In **13e**, when the –H at 4-position of the piperidine ring was replaced by a $-CH_3$ resulting in analogue **13f**, the activity was enhanced to twofold against *A. flavus* and *A. niger*, whereas, the activity remained unchanged against *C. albicans*.

Table 2. Antifungal activities of 2-amino-9-[2-substituted-4-(4-substituted piperidin-1-sulfonyl) phenyl]-1,9-dihydropurin-6-ones (**13a–13h**)

Compound	X	Y	MIC, $\mu g\,mL^{-1}$		
			A. flavus	*A. niger*	*C. albicans*
13a	H	H	—	—	—
13b	H	CH_3	—	—	—
13c	F	H	—	—	—
13d	F	CH_3	64	32	64
13e	Cl	H	64	64	64
13f	Cl	CH_3	32	32	64
13g	OCH_3	H	16	16	32
13h	OCH_3	CH_3	16	32	32
Griseoflavin-16			16	16	8

On the other hand, replacement of the –Cl by a $-OCH_3$ (**13g**) remarkably enhanced the activity against all the fungal strains. Against *A. flavus* and *A. niger*, **13g** displayed activity at a minimum inhibitory concentration of 16 $\mu g\,mL^{-1}$. In **13g**, substitution of a $-CH_3$ on the 4-position of the piperidine ring (**13h**) showed no difference in the activity compared to **13g** against *A. flavus* and *C. albicans*, whereas the $-CH_3$ substitution caused a profound drop in the activity to the level lower than that of **13g**.

In summary, syntheses of guanylsulfonamides, 2-amino-9-[4-(piperidin-1-sulfonyl)phenyl]-1,9-dihydropurin-6-ones, were accomplished by the combination of three synthon components. Firstly, the equivalent of synthon **B**, the compound **6**, was synthesized by the condensation of guanidine and diethyl malonate, followed by chlorination, hydrolysis, and nitration reactions. Secondly, the equivalent of synthon **C**, the compounds **10a**–**10h**, was synthesized by acetylation of anilines, followed by chlorosulfonylation, condensation, and hydrolysis reactions. Eventually, substitution reaction between **6** and **10a**–**10h** followed by reductive aminoformylation and intramolecular cyclization reactions afforded the guanylsulfonamide **13a**–**13h**, respectively. Most of the target chemical entities **13a**–**13h** exhibit modest antibacterial and antifungal activities against a wide spectrum of pathogenic bacterial and fungal strains. Particularly, the guanylsulfonamides **13e** and **13f** with –Cl displayed better antibacterial efficacy than that of the standard drug Norfloxacin against *S. aureus* and *S. faecalis*, while **13e** showed antibacterial efficacy akin to that of Norfloxacin against *P. aeruginosa*. Against the fungal strains *A. flavus* and *A. niger*, the guanylsulfonamides **13g** and **13h** carrying $-OCH_3$ exhibited antifungal potency akin to that of the standard drug Griseoflavin-16 except **13h** against *A. niger*. The appreciable antibacterial and antifungal efficacies of the new guanylsulfonamides deserve further investigation in order to establish the mode of action.

Acknowledgment

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Supplementary data

Experimental details and characterization data for compounds **8a**–**8d**, **9a**–**9h**, **10a**–**10h**, **11a**–**11h**, **12a**–**12h**, and **13a**–**13h.** Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.09.060.

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