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Synthesis and biological evaluation of some drug-like scaffolds of benzo-and pyrido-fused medium-sized *N*-heterocycles obtained via intramolecular Friedel-Crafts acylation reactions

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Abstract: An unprecedented, concise and environmentally-friendly protocol for the synthesis of benzo-and pyrido-annulated azocinones, azoninones and azecinones **8a-h** via Friedel-Crafts reactions is described. These simple and efficient procedures involve cycliacylations of heterocyclic esters **7a-h** in the presence of catalytic amount of $AlCl_3/CH_3NO_2$ or TfOH or PPA catalysts as the key step. Starting amides **3a-d** were readily obtained by coupling reactions of acryloyl chlorides **2ab** with pyridin-2-amines **1a,b**. Our developed strategy offers some high selectivity reactions, mild reaction conditions and easy access to complex medium-sized *N*-heterocycles in moderate to good yields. All tetracyclic fused compounds have been screened for antimicrobial activity.

Keywords: Friedel-Crafts cycliacylations; Brønsted acid; azocines; azoninones; azecinones.

INTRODUCTION

Condensed medium-sized *N*-heterocycles containing azepines, azocines and azonines are widely found in pharmacologically active natural products[1] and often incorporated into drugs.[2] A few examples are given in Figure 1. Interestingly, their aryl- and heteroaryl derivatives are particularly noted for their diverse biological activities[3] and in many industrial applications such as polymers[4] organic semiconductors and luminescent materials.[5]

Despite the high transannular strain,[6] enthalpic and entropic barriers[7] of encountered in the synthesis of nitrogen containing ring systems, the last few decades have witnessed a much efforts have been dedicated to developing methods for the construction of such ring systems.

In the literature, a variety of well-established methods are used for the synthesis of medium-sized *N*-heterocycles of various ring sizes include well known, transition-metal mediated cyclizations and annulations,[8] ring-closing

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metathesis (RCM),[9] Tandem cleavage-cyclizations,[10] sigmatropic cyclizations,[11] radical-mediated ring expansions and fragmentations,[12] Fischer carbene complexes (FCCs),[13] Diels-Alder reactions,[14] domino cycloadditions[15] and Cope rearrangements.[16]

On the other hand, a significant number of cases are described in the literature related to construction and isolation of benzo-annulated azonines and higher ring systems as in the total synthesis of dopamine antagonists, erythrina and vincristine alkaloids.[17]

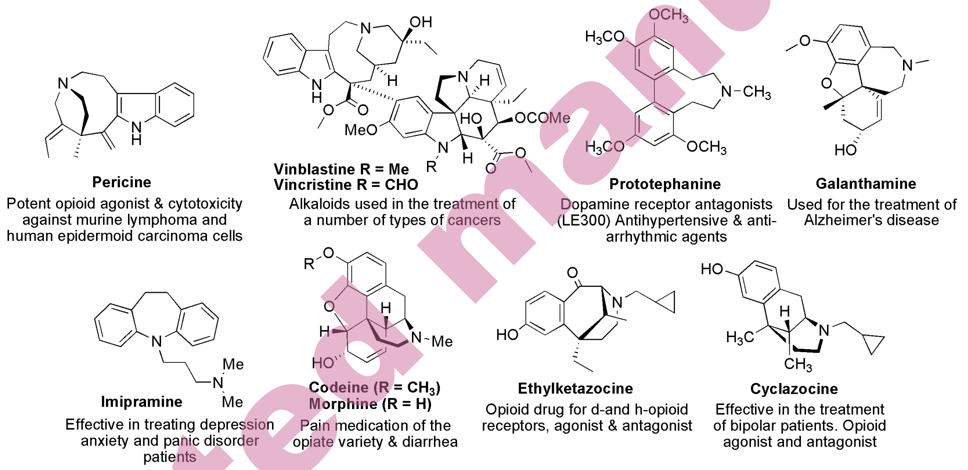


Figure 1. Some of biologically active alkaloids containing medium-sized *N*-heterocycles.

Some the most commonly used methods for the construction of polycyclic azonines include, the Beckmann ring expansion of unsymmetrical oximes,[18] biosynthesis of (s)-*N*-benzylisoquinolines and their dienone derivatives,[19] Schmidt rearrangement of alicyclic ketones,[20] ring-closing metathesis (RCM) of 2-pentenylphenyl-*N*-benzamides,[21] Fischer indolization of 1,2,3,4-tetrahydrocarbazole phenylhydrazones,[22] acyloin condensation of diesters,[23] asymmetric induction by the addition of Grignard reagents to phenylglyoxylate derivatives of the phenyldihydrothebaine alkaloids[24] aza-Claisen rearrangement of α-silyloxyamides mediated by lithium hexamethyldisilazide (LHMDS) in toluene,[25] fragmentation/acylation reactions of enol-ether of dihydropyridone[26] and coupling of palladated 3-phenylpropanamides with alkynes followed by CO-insertions.[27]

Given the wide array of biologically and industrial applications of *N*-heterocycles, a flexible route to access these types of structures from readily available acyclic precursors would be attractive. Recently we have studied the formation of a diverse drug like *Carb*-and heterocycles[28-30] via intramolecular Friedel-Crafts[31] methodology with broad functional group compatibility. In continuation of our research activity on polyfunctionalized heterocyclic systems, herein, we wish to report the synthesis of newly fused and bridged nitrgen containing [6,(6/7),(8/9/10),6]-ring systems namely; benzo-and pyrido-annulated azocinones, azoninones and azecinones via Friedel-Crafts cycliacylation reactions of nitrogen containing ester precursors. Furthermore, these polycyclic substrates were tested against bacteria and fungi.

EXPERIMENTAL

General: Commercially available reagents were used without further purification unless otherwise stated; solvents were dried by standard procedures. Melting points were taken on a digital Gallenkamp capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer using KBr wafer and thin film techniques (ν cm^{-1}) and are in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL LA 400 MHz FT-NMR (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) using $CDCl_3$ solvent with tetramethylsilane (Me_4Si, TMS) as internal standard. Chemical shifts are given in parts per million (δ), and the coupling constants (*J*) are given in Hertz (Hz), respectively. Mass spectra were measured on a Perkin Elmer PE SCIEX-API 2000 mass spectrometer at an ionizing potential of 70 eV using the direct inlet system. Elemental analyses were carried out by a GmbH Vario EL III, 2400, CHNOS-elemental analyzer. Antimicrobial screenings were performed at Assiut University Mycological Center (AUMC) in DMF by disc diffusion. The progress of reactions was accomplished by thin-layer chromatography (TLC) analysis on coated silica plates (Silufol, UV-254 TLC, aluminum sheets) and plates were visualized with UV light (at 254 and/or 360 nm). Flash column chromatography was performed on silica gel (230–400 mesh) or basic alumina using AcOEt and hexane as eluents. The 3–(pyridin–2–yl)acryloyl chloride **2b** was obtained by refluxing a mixture of 3-(pyridin-2-yl)acrylic acid (Lit.[33] mp 233–236 °C) with excess PCl_5 in benzene for 5 h on a water bath.

Analytical and spectral data are given in the Supplementary material to this paper.

Chemistry

*General procedure for synthesis of arylamides (**3a-d**).* A solution of acid chloride (cinnamoyl chloride **2a** or 3–(pyridin–2–yl)acryloyl chloride **2b** (32 mmol) in benzene (20 mL) was added dropwise with stirring over a period of 30 min to a solution of amines **1a** or **1b** (30 mmol) in dry benzene (30 mL) containing a catalytic amount of pyridine (0.5 mL). The resulting mixture was stirred at room temperature for 4 h, and then refluxed on a steam bath for 3 h. The mixture was cooled and the solvent was then concentrated in *vacuo*. After standing, the resulting solid was filtered to give the crude amides. The residue was purified by flash chromatography (basic alumina, AcOEt/hexane, 1:1) to afford pure amides **3a-d**. Further purifications and yields are given in spectral data.

*General procedure for synthesis of lactams (**4a-d**).* A mixture of amide **3a-h** (20 mmol) with anhydrous $AlCl_3$ (50 mmol) and NaCl (5 g) was warmed with stirring at 80-90 °C for 1h. After which TLC analysis (EtOAc/*n*–hexane, 1/3) indicated that the reaction was complete, the resulting hot mixture was poured into an excess of well–stirred ice water (150 mL) and then basified with NaOH solution (40 mL, 20%). The mother liquor was diluted with water (100 mL) and extracted with EtOAc (3×30 mL). The combined extracts were washed with water, dried over $MgSO_4$ and filtered. The solvent was removed in *vacuo* gave a crude product. Purification by flash column chromatography (basic alumina, EtOAc/*n*–hexane, 1/1) to give pure products **4a-d**. The yields and spectral data are given in spectral data file.

*General procedure for synthesis of bicyclic amines (**5a-d**).* To an ice-cold stirred suspension of $LiAlH_4$ (30 mmol) in ether (40 mL), was added a solution of lactam **4a-d** (10 mmol) in THF (30 mL) dropwise with efficient stirring over a period of 30 min. The mixture was stirred at room temperature for 2 h and then refluxed for 4 h on water bath. After cooling in ice-bath, excess hydride was carefully destroyed by sequential addition of cold water (5 mL) and aqueous NaOH solution (20 mL, 10%) with efficient stirring. The resulting suspension was stirred for 30 min. After filtration and washing the precipitate with AcOEt, the precipitate was discarded and the filtrate was extracted with AcOEt (3×30 mL). The combined organic phase was washed with water, $NaHCO_3$ (30 mL, 5%), and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure gave a dark crude products **5a-d**. Purification by flash column chromatography (basic alumina, EtOAc/*n*–hexane, 1/1) to afford the target amines **5a-d**. Purifications and yields are given in spectral data file.

*General procedure for the synthesis of heterocyclic esters (**7a-h**).* A solution of ethyl 2–bromoacetate **6a** or ethyl 3–bromopropanoate **6b** (20 mmol) in DMF (15 mL) was added dropwise with efficient stirring over 10 min to a mixture of bicyclic amine **6a-d** (15 mmol) and milled K_2CO_3 (40 mol) in DMF (30 mL) at room temperature. The reaction mixture was refluxed for 8–10 h. After which TLC analysis (AcOEt/hexane, 1/2) showed the reaction to be complete, the solvent was removed in *vacuo* and the residue was diluted with water (100 mL) and extracted with AcOEt (3×30 mL). The combined organic layer was washed with water, dried over $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography column to afford crude ester **7a–h**. Crystallization, yields and spectral data are given in spectral data file.

*General procedure for cyclization of heterocyclic esters **8a-h***

*Method I: General Procedure for $AlCl_3/CH_3NO_2$– mediated cyclizations of esters (**8a-h**).* To a solution of $AlCl_3$ (10 mmol) in CH_3NO_2 (100 mmol) was added a solution of ester **7a-h** (3 mmol) in DCM (10 mL) was added dropwise with constant stirring over 10–15 min at ambient temperature. The mixture was stirred for a certain time at the required temperature (Table I). Afterwards, the mixture was quenched with ice–cold HCl solution (30 mL, 10 %) and extracted with EtOAc (2×30 mL). The combined extract was washed with H_2O and Na_2CO_3 solution (30 mL, 5%). After drying over $MgSO_4$, the solution was filtrated and evaporated under reduced pressure to give the crude products **8a-h**.

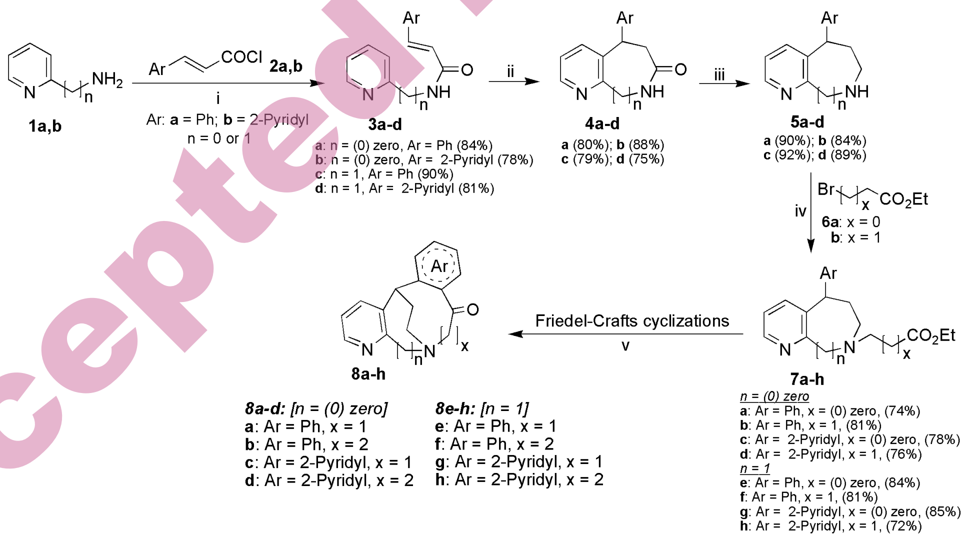
*Method II: General Procedure for TfOH- mediated cyclizations of esters (**8a-h**).* To a cooled (0 °C) solution of esters **7a-h** (3 mmol) in DCM (15 mL) was added TfOH (12 mmol) dropwise over 10 min and the mixture was stirred at the required temperature and time as shown in Table I. Thereafter, the mixture was cooled and then quenched cautiously by the slow addition of aqueous $NaHCO_3$ solution (40 ml, 30%). The product was extracted with EtOAc (3×30 mL). The organic extracts were washed with water and Na_2CO_3 solution (30 mL, 5%), dried over anhydrous Na_2SO_4 and then evaporated in *vacuo* to give the crude products **8a-h**.

*Method III: General Procedure for PPA-mediated cyclizations of esters (**8a-h**).* To a solution of esters **7a-h** (3 mmol) in PhCl (15 mL), was added freshly prepared PPA (10 g) and the mixture was refluxed for the required time presented in Table I. Afterwards, the solvent was evaporated under reduced pressure. The cold mixture was made alkaline with $NaHCO_3$ solution (40 ml, 20%) and then extracted with EtOAc (3×30 mL). The combined organics was washed with water and Na_2CO_3 solution (30 mL, 5%). After drying over $MgSO_4$, the solution was filtered and concentrated in *vacuo* to afford the desired crude products **8a-h**. In all procedures, the completion of the reaction was monitored by TLC-analysis. The crude residue was subjected to flash chromatography (basic alumina, EtOAc/hexane, 1/2) to afford the pure cyclic products **8a-h**. Further crystallization and yields are given in and spectral data file.

RESULTS AND DISCUSSION

Chemistry

The reaction sequences employed for synthesis of polyheterocycles **8a-h** from heterocyclic esters **7a-h** are illustrated in Scheme 1. Firstly, the starting amides **3a** (n = 0; Ar = Ph), **3b** (n = 0; Ar = 2-Pyridyl), **3c**[32] (n = 1; Ar = Ph), **3d** (n = 1; Ar = 2-Pyridyl), were obtained in good yields through the reaction of ary-substituted acryloyl chlorides (**2a:** Ar = Ph; **2b:** Ar = 2-Pyridyl[33]) with pyridine amines **1a,b** in benzene for 7 h. Secondly, these amides were transformed to the corresponding bicyclic lactams **4a-d** by fusion with $AlCl_3$/NaCl at 80-90°C for 1h following the standard literature procedure.[34] Thirdly, reduction of the latter lactams **4a-d** using $LiAlH_4$ in Et_2O/THF for 4-6 h under reflux conditions to furnish bicyclic amines **5a-d**. Various substituted esters **7a-h** were synthesized *via* *N*-alkylations of bicyclic amines **5a-d** with ethyl 2-bromoacetate **6a** or ethyl 3-bromopropanoate **6b** in the presence of K_2CO_3 in DMF.



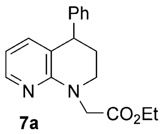
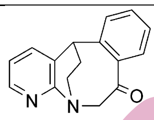
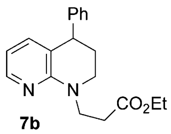
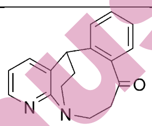
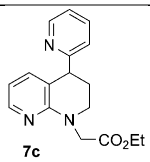
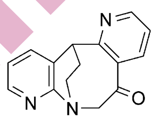
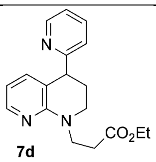
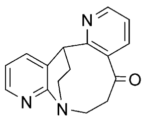
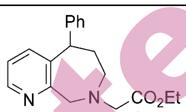
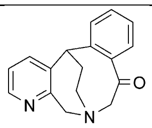
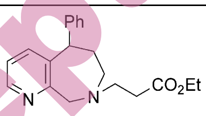
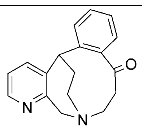
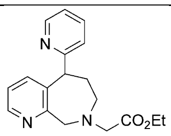
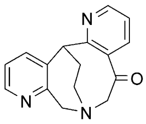
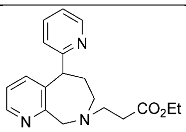
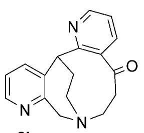
Scheme 1. Reagents and conditions: (i) cinnamoyl chloride or 3-(pyridin–2–yl)acryloyl chloride/PhH, 7 h, reflux, (ii) $AlCl_3$/NaCl, 1h, 80-90°C, (iii) $LiAlH_4$/THF/Et_2O, reflux, 4-6 h, NaOH, (iv) $BrCH_2CO_2Et$ or $BrCH_2CH_2CO_2Et$/K_2CO_3/DMF, reflux, 8-10 h, (vii) Cycliacylations of esters **8a-h** mediated by $AlCl_3$/CH_3NO_2 or TfOH or PPA promoters (Table I).

Our synthetic approach allows easy access to fused medium-sized *N*-heterocycles **8a–h** namely, benzo-fused pyrido[2,3-b:2',3'-*e*]azocinones, pyrido[2,3-*b*]azoninones and pyrido[2,3-c:2',3'-*f*]azecinones (Table I). Initially, an investigation of $AlCl_3/CH_3NO_2$ or TfOH or PPA catalysts in cycliacylations of nitrogen-based esters **7a-h** was carried out under different reaction conditions. We focused on the screening of several variables included, mole ratio, catalyst type and loading, solvent and temperature. Interestingly The choice of Brønsted and Lewis acids screened was based on the degree of oxophilicity, chemical yield as well as extent of their acidity.

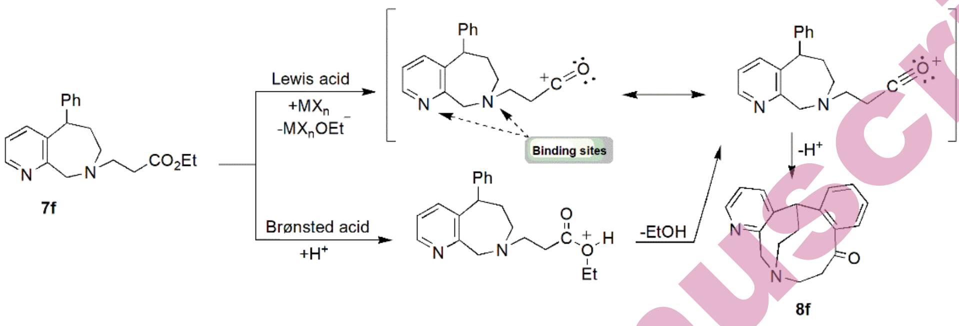
Interestingly, in this type of electrophilic aromatic substitution reactions containing sufficiently electron rich nucleophiles, it is clearly the appearance of catalytic inhibitions[35] by sp^2-and sp^3-hybridized nitrogens beside the presence of poor leaving -OEt group present in cyclization precursors **7a-h**. These coordination or protonation of basic nitrogen with acidic promoters leading to ring closure is difficult to occur or gave disappointingly low yields. Practically, low yields of tetracyclic amines **8a-h** were obtained on cyclization of precursors **7a-h** with less than equivalent of these catalysts at lower reaction time. It was observed that, cycliacylations of electron rich precursors and yield enhancements were attained under sever conditions with more than stoichiometric loading of oxophilic promoter for longer reaction times and high temperatures.

On the other hand, numerous studies on the intramolecular Friedel-Crafts acylation mechanisms have been carried out.[36-38] Thus, it can be concluded that, cyclization mechanism of highly electron-rich precursors diverges to two different pathways based on the nature of the acylating agent and the binding strength of acidic promoters on substrate heteroatoms. A possible mechanism for formation of the compound **8f** is shown in Scheme 2. The cycliacylation mechanism of this reaction is probably similar to that of the Okauchi acylation procedure.[36] It is presumably that, differential in cyclization pathways is due to whether heteroatoms on acyclic ester **7f** were protonated by Brønsted acid proton or the formation of a polarized Lewis acid-acylating agent complex. This coordination's were leading to either alteration in catalyst acidity or reduce its reactivity beside deactivation of a nucleophilic substrate. It was hypothesized that, the nature of the acylating agent and the strength of the Lewis acid determine the electrophilicity of this complex while the regiochemistry is determined by the transition state.

TABLE 1. Optimization of Friedel-Crafts cyclizations of precursors 7a-h.

Entry	Substrate	Methods	Time, h	Product	Yield (%)
1	 **7a**	Method I* Method II** Method III***	12 8 8	 **8a**	82 75 71
2	 **7b**	I II III	15 5 7	 **8b**	80 73 70
3	 **7c**	I II III	18 6 10	 **8c**	84 77 74
4	 **7d**	I II III	11 8 12	 **8d**	88 81 71
5	 **7e**	I II III	16 10 10	 **8e**	84 80 72
6	 **7f**	I II III	18 7 10	 **8f**	91 78 68
7	 **7g**	I II III	18 6 8	 **8g**	90 87 72
8	 **7h**	I II III	15 6 10	 **8h**	89 86 74

*Method I: esters **7a**–**h** (3 mmol) in CH_2Cl_2 (10 ml), $AlCl_3$ (10 mmol), $MeNO_2$ (100 mmol), room temperature.
Method II: esters **7a–**h** (3 mmol), TfOH (1 ml, 12 mmol), 1,2-DCE (20 ml), reflux.
***Method III: esters **7a**–**h** (3 mmol), PPA (10 g), PhCl (15 mL), reflux.



Scheme 2. Proposed mechanism for the cyclization of ester **7f** by Lewis or Brønsted acids.

Subsequently, that would lead to removal of EtOH molecule generating acyl-carbocation either free or as an ion pair.[39] The anticipated acyl-carbocation stabilizes both by resonance delocalizations and adjacent hyperconjugative interactions. Ultimately, ring closures of this carbocation may proceed via a single transition states concurrent with the removal of H^+ to give the product **8f** in a single regioisomer.

Further evidence for this result was confirmed from NMR spectroscopy. A closer look at the intermediates **7a-f** and cyclic structures **8a-h**, we observed that the benzylic-carbon (C-5) is a chiral center and the next methylene group (C-6) its protons are diastereotopic[40] in nature. These protons are chemically inequivalent and will split each other resulted in complex overlapping signals with different multiplicities. In addition to diastereotopic protons and because of the flexibility of these ring systems, other constitutional conformers with inequivalent sets of cyclic methylene protons (pseudo-axial and equatorial hydrogens) resulted from a large number of low energy interconverting conformers. Interesting stereochemical outcomes were observed during this study. Since cyclization precursors and products were contains the chirality as well as conformer mixtures with different chemical environments, NMR interpretation was difficult. As a result, some efforts performed to understand the reactivity profiles of these building blocks and to identify the configuration of unique structures and bonding characteristics of these ring systems. The assignment of all chemical structures of the cyclic products was made on the direct inspection of the ^{1}H NMR spectrum.

For example, the ^{1}H NMR spectrum of compounds **7f** and tetracyclic **8f** displayed complex signals of CH_2-group adjacent to the stereogenic center and bridged pseudo-axial and equatorial protons. Moreover, the neighboring environment of bridged *N*-CH_2 group is very unsymmetrical due to the ring conformations. The expected downfield shifting signal for pseudo-equatorial could be explained in terms of shielding effect exerted by the magnetic anisotropic effect generated by heteroatoms of both carbonyl groups and *N*-heteroatoms incorporated in tetracyclic structures.

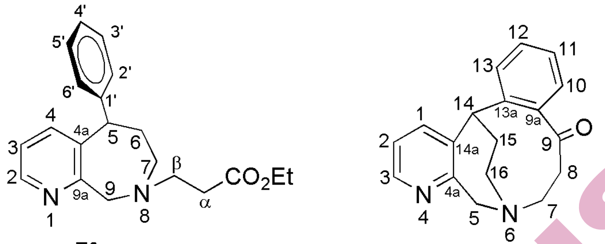


Figure 3. Diastereotopic protons containing tetracyclic structure **8f** and its acid precursor **7f**

Thus, the ^{1}H NMR spectrum of **7f** showed three upfield triplet signals at δ 1.18, 2.48 and 2.93 ppm related to $\underline{CH_3}CH_2O$-, $C^{\alpha}H_2$ and $C^{\beta}H_2$ groups. The most downfield quartet signal at δ 4.28 ppm was assigned to the $CH_3\underline{CH_2}O$-group. The complex overlapped multiplets at δ 2.05 ppm is assigned to the diastereotopic protons (Ha & Hb) of C^6H_2-group appeared as doublet of doublets of doublets of doublets (dddd) with four vicinal coupling constants 13.9, 6.6, 4.7 and 2.6 Hz. Another upfield multiplet signal at δ 2.91 ppm is assigned to C^7H_2 group appeared as doublet of doublets of doublets with coupling constants 7.8, 6.6 and 2.6 Hz. Whilst, two signals appeared at δ 4.01 and 4.17 ppm are assigned to C^7H and *N*-C^9H_2, respectively. These upfield shifts can be explained by shielding due to the magnetic anisotropic effect[49] generated by heteroatom or the carbonyl group. The remaining eight aromatic protons appeared in the range of δ 7.10-8.60 ppm with inner overlapping and different multiplicities.

In comparison with ester **7f**, the ^{1}H NMR spectrum of tetracyclic skeleton **8f** displayed as several complex overlapped signals. The most upfield with multiplicity of doublet of doublets of doublets of doublets at δ 2.66 ppm is assigned to the bridged-$C^{15}H_2$ with couplings 11.1, 7.7, 6.3 and 2.2 Hz. The complex multiplet signals in the regions of δ 3.08-3.10, 3.32-3.41 and 3.48-3.50 ppm were assigned to C^8H_2, bridged-*N*$C^{16}H_2$ and C^7H_2 groups, respectively. Chemically inequivalent C^5H_2-protons are expected to appear in the range of δ 4.37-4.48 ppm as doublet of doublets with coupling constants 8.6 and 6.9 Hz. A doublet signal appeared at δ 4.45 ppm is assigned to bridged-$C^{14}H$ proton. The diagnostic signal in the ^{13}C NMR spectrum of **8f** is that of the carbonyl carbon at δ 200.8 ppm. The upfield signals at δ 31.2, 32.9, 35.9, 51.4, 53.4 and 59.5 ppm are assigned to $C^{14}H$, bridged-CH_2, C^8H_2CO, C^7H_2, C^5H_2 and bridged-$C^{16}H_2$, respectively. Comparison of the fragmentation patterns of compounds ester **7f** with tetracyclic **8f** show some quantitative and qualitative differences attributed to the nature of both the substituents at the 5-position of the bicyclic ring system and at the nitrogen atom. The mass spectra of ester **7f** are much simpler and contain only molecular ion peaks *m/z* 324 with intensity 20% and the base peak appeared at *m/z* 279. Whilst, the molecular ion peak of **8f** appeared at 278 as a base peak (100%).

Evaluation of antimicrobial activity

The antimicrobial activity of the synthesized compounds **8a-h** was determined *in vitro* against a variety of bacteria and fungi. For antibacterial activity was investigated against Gram-positive bacteria *(Bacillus Subtilis*, *Micrococcus luteus)* and Gram-negative bacteria *(Escherichia coli*, *Pseudomonas aeruginosa*) using Chloramphenicol (0.001 mole/ml) as standard. The antifungal activity was determined against *Aspergellius flavus, Candida albicans, Geotrichum candidum* and *Scopulariopsis brevicaulis* using Clotrimazole (0.001 mole/ml) as standard. The tests were carried out using disc diffusion method.[41] The minimum inhibitory concentrations (*MICs*) for compounds were calculated in DMF/H_2O solution and activity mentioned on 1000 ppm.

The results are summarized in Table II. Amongst the compounds tested for antibacterial activity, compounds **8c, 8d, 8g** and **8h** possess good activity against all the bacteria, whereas compounds **8a**, **8b**, **8e** and **8f** were found to display moderate activity against *M.luteus, E.coli and P.aeruginosa and* low activity against Gram +ve bacteria (*B.cereus*).

TABLE II. Antimicrobial activity of the compounds **8a-h**

Compd.[A] no.	Antibacterial activity zone of inhibition in mm[B] Gram positive (+ve)		Gram negative (-ve)		Antifungal activity zone of inhibition in mm			
	B. cereus	*M. luteus*	*E. coli*	*P. aeruginosa*	*A. flavus*	*C. albicans*	*G. candidum*	*S. brevicaulis*
8a	7	10	15	14	10	11	10	11
8b	5	16	12	13	11	10	13	16
8c	44	37	22	52	16	14	13	15
8d	25	16	19	26	10	17	12	12
8e	6	15	17	20	13	11	10	13
8f	9	17	20	18	15	13	14	10
8g	58	39	36	64	22	19	24	31
8h	37	28	38	45	13	26	15	36
Standard[C]	20	23	22	22	26	22	20	25

[A]Chemical compounds tested at 20 mg.
[B]The minimal inhibitory concentrations (MIC, 50μg/ml) for each pore in DMF/H_2O
[C]Standard for antibacterial: Chloramphenicol (0.001 mole/ml). Standard for antifungal: Clotrimazole (0.001 mole/ml).

From the data presented in Table II, it was observed that compounds **8c, 8d, 8g** and **8h** show good activity against all fungal strains as compared to standard Chloramphenicol. Other compounds **8a, 8b, 8e** and **8f** showed moderate antifungal activity. Further, it could be concluded that, due to the increasing of ring size and the insertion of additional pyridine nucleus in a complex molecular structures, compounds **8g** and **8h** showed relatively better inhibitory activity towards all the tested microorganisms than compounds **8c** and **8d**.

CONCLUSIONS

In summary, the present work embodies a facile and concise synthesis of several of benzo-and pyrido-fused azocinones, azoninones and azecinones incorporating 8-, 9-and 10-membered *N*-heterocyclic rings from easily assessable ester precursors in good to excellent yields via Friedel-Crafts cycliacylation methodology. The newly synthesized scaffolds **8a-h** have been assayed for their bactericidal and fungicidal activities. The combination of structural complexity and biological activity of tetracyclic skeletons **8a-h** has made these fused ring systems as important architectures for the promising drug discovery. The simplicity and wide variability of the methods makes it a good alternative to the literature lengthy multistep procedures usually employed.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: https://www.shd-pub.org.rs/index.php/JSCS/article/view/13466, or from the corresponding author on request.

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И З В О Д

СИНТЕЗА И ИСПИТИВАЊЕ БИОЛОШКЕ АКТИВНОСТИ НЕКИХ СТРУКТУРА СЛИЧНИХ ЛЕКОВИМА КОЈЕ САДРЖЕ БЕНЗО- И ПИРОДО-КОНДЕНЗОВАНЕ *N*-ХЕТЕРОЦИКЛЕ СРЕДЊЕ ВЕЛИЧИНЕ, ДОБИЈЕНИХ ИНТРАМОЛЕКУЛСКОМ РЕАКЦИЈОМ ФРИДЕЛ-КРАФТСОВОГ АЦИЛОВАЊА

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Приказан је јединствен и еколошки прихватљив поступак за синтезу бензо- и пиридо-кондензованих азоцинона, азонинона и азецинона **8a-h** применом Фридел-Крафтсове реакције. Овај једноставан и ефикасан поступак, као кључни синтетички корак, има циклоациловање хетероцикличних естара **7a-h** у присуству каталитичке количине $AlCl_3/CH_3NO_2$, TfOH или PPA. Полазни амиди **3a-d** су лако добијени куплавањем акрилоил-хлорида **2a** и **2b** са пиридин-2-аминима **1a** и **1b**. Наша примењена стратегија нуди реакције високе селективности, благе реакционе услове и лак приступ сложеним *N*-хетероциклима средње величине, у средњем до добром приносу. Испитана је антимикробна активност свих тетрацикличних кондензованих једињења.

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