Abass, Mohamed; Ismail, Mostafa M.; Abdel-Monem, Wafaa R.; Mayas, Aisha S. 
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Journal of the Mexican Chemical Society, vol. 53, núm. 2, 2009, pp. 48-54
Sociedad Química de México
Distrito Federal, México

Disponible en: http://www.redalyc.org/articulo.oa?id=47512080002
Substituted Pyridopyrimidinones. Part 3. Synthesis of Some Novel Ether Derivatives of 4H-Pyrido[1,2-a]pyrimidin-4-one

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Received May 29, 2009; accepted June 25, 2009

J. Mex. Chem. Soc. 2009, 53(2), 48-54 © 2009, Sociedad Química de México ISSN 1870-249X

Abstract. A series of novel bis-heterocyclic ethers, containing 4H-pyrido[1,2-a]pyrimidin-4-one along with other five and six-membered heterocyclic rings, was obtained utilizing ethyl [(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetate (1), [(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetic acid (2) and/or [(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetohydrazide (3). Reaction of ester 1 with some ortho-hydroxy-aldehydes furnished the corresponding pyrido-pyrimidyloxypyrones. Reaction of ester 1 or acid 2 with 1,2-diamines led to some imidazoles. Also, some pyrazole, triazole, and oxadiazoline derivatives have been prepared from hydrazide 3.

Key words: Pyrido[1,2-a]pyrimidinone, Ethers, Pyrazoles, Oxadiazolines, Pyrones.

Introduction

The group of pyrido[1,2-a]pyrimidin-4-ones is a well-known class of aza-bridgehead fused heterocyclic compounds which have miscellaneous pharmaceutical applications [1]. For example, this structural pattern is present in the known psychotropic agents risperidone and paliperidone [2,3], the human leukocyte elastase inhibitor SSR69071 [4], the antiallergic agent ramastine [5], and the antioxidants 2-arylpyrido[1,2-a]pyrimidin-4-ones [6] (Figure 1). As a continuation to our previous work [7], we utilized ethyl [(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetate (1) to obtain novel bi-heterocyclic ethers which are of expected antipsychotic activity. This expected biological activity may be due to the presence of pyridopyrimidinone and other known biologically active heterocycles such as pyrazole, imidazole, triazole, oxadiazole, pyrone, coumarin, and quinolinone in one-molecular frame [8,9].

Results and Discussion

The chemistry of carboxylic acids and their hydrazides is very interesting due to the capability of both carboxylic and hydrazide functions to be transformed to different azoles and azines [10]. This prompted us to convert the readily available ester 1 [7] to its corresponding free acid and acid hydrazide and thence use of both to obtain the claimed heterocycles. Saponification of the ester 1 smoothly furnished the corresponding 2-substituted acetic acid derivative 2. The acetohydrazide 3 was obtained from the hydrazinolysis of the ester 1 (Scheme 1).
**Knoevenagel** reaction of α-active methylene esters with ortho-hydroxy-aldehydes was reported as facile synthesis of condensed α-pyranoles and coumarins [11]. Thus, the reaction of the ester I with salicylaldehyde was performed by heating in ethanol containing piperidine as the catalyst, to give 2-[(2-oxo-2H-chromen-3-yl)oxy]-4H-pyrido[1,2-a]pyrimidin-4-one (6) (Scheme 2). IR spectrum shows evidences for this cyclization by exhibiting two absorption bands at ν 1720 and 1691 cm⁻¹ corresponding to α-pyranoles and γ-pyrimidinone carbonyls, respectively. In addition, ¹H NMR spectrum displays specific signals for α-pyridine proton at position-5 appeared as doublet at δ 8.97 while the singlet due to proton at position-3 is shown at δ 5.46. The signal of proton at position-4 of α-pyridine is observable at δ 8.43 as a singlet. Similarly the ester 1 was subjected to react with 2-hydroxy-4-oxo-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (4) [12] to afford the ether 7. Also, reaction of the ester 1 with 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoine-3-carboxaldehyde (5) [13], under the same conditions, led to the formation of 6-methyl-3-[(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]-2H-pyran-3,2-cquinolone-2,5(6H)-dione (8) (Scheme 2). The mass fragmentation pattern of compound 7 evidences the proposed structure as illustrated herein (Chart 1).

Thermal condensation of the ester 1 with triethyl orthoformate was carried out to prepare the corresponding ethyl 3-ethoxyacrylate derivative, which is considered promising synthon for different diazoles and diazines. Indeed, this intermediate ethoxyacrylate was not separated. The elemental analysis reveals that the formula is less than the expected by the intermediate ethoxyacrylate. Consequently, the ester 1 was treated with carbon disulfide, in presence of ethanolic potassium hydroxide, followed by thermal cyclization in about 7% yield. This relatively low yield may be attributed to thermal decarboxylation of the acid 2 before condensation takes place. Much better yield (55%) was obtained from the reaction with ester 1. Thermal cyclocondensation of the acid 2 with 1,2-phenylenediamine led to the formation of 2-[(1H-benzimidazol-2-yl)-methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (11) in 64% yield. This reaction was carried out thermally in absence of solvent and interestingly, when we try to use the ester 1 under the same conditions the yield was not satisfactory. The structure of compound 11 was inferred from its IR, ¹H NMR spectral data and elemental microanalysis. Benzoxazole 12 and benzoazole 13 were obtained starting from the acid 2 and 2-amino phenol or 2-aminothiophenol, under the same conditions. Recently, 1,2,4-triazoles showed potential biological activity [14]. So that it was planned to prepare a compound containing both of pyridopyrimidine and 1,2,4-triazole in one molecular-frame. Thus, cyclocondensation of the acid 2 with thiocarboxhydrazide afforded 2-[(4-amino-5-thioxo-4,5-dihydro-1H-2,4-triazol-3-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (14). Moreover, the triazole 14 was conveniently prepared by stepwise treatment of hydrazide 3 with carbon disulfide, in presence of ethanolic potassium hydroxide, followed by in situ addition of hydrazine hydrate to perform cyclization of the presumed potassium diithio intermediate (Scheme 3).

Thermal cyclization of the acetoxyhydrazide 3 with triethyl orthoformate, in boiling DMF or in absence of solvent, smoothly afforded pyrazolinone 15. The spectral data of the
product 15 revealed the disappearance of both NH$_2$ and OCH$_2$ groups, indicating their evolution in cyclization process. 2-[(2-Methyl-5-methylthio-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)oxy]-4H-pyrido[1,2-a]pyrimidin-4-one (17) was characterized as the product obtained when hydrazide 3 was treated with carbon disulfide and excess amount of methyl iodide with $^1$H NMR spectrum of compound 17, revealed presence of two types of methyl groups at δ 2.61 due to (SCH$_3$) and δ 3.41 due (NCH$_3$) and absence of specific signal for (OCH$_2$CO). The characteristic IR stretching bands at ν 1688 and 1651 cm$^{-1}$ shows the occurrence of C=O groups due to pyrazolinone and pyridopyrimidinone systems. Formation of the compound 17 is thought to be through the expected intermediate N-methyl-N$'$-[di(methylthio)methylene]-2-[(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetohydrazide (16) which was not isolated (Scheme 4).

The reaction of hydrazide 3 with benzaldehyde, or 4-hydroxybenzaldehyde, or 4-nitrobenzaldehyde was carried out in the presence of piperidine in boiling ethanol. It is anticipated that this reaction would lead to the corresponding benzal hydrazones. Elemental microanalysis was in good accordance with this expectation. IR and $^1$H NMR of the compound 18b (R=OH) revealed that this hydrazone is present in a cyclic form. Thus, we observed two singlets at δ 5.02 and 5.80 due to a benzal proton and a β-pyrimidine proton, respectively along with a deuterium exchangeable proton at δ 8.13, which is attributed to an oxadiazoline (N–H) resulted from ring–chain tautomeration. The azomethine proton that characterizes the open chain hydrazone was merely noticed at δ 8.54 with relative integration 1:9, compared with proton at δ 5.02. IR spectrum of compound 18b revealed additional evidence where ν$_{C=O}$ of hydrazide that was present in start compound 3 is obviously no longer observed. Building on these observations, it was concluded that the products should be 2-[(5-aryl-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-ones 18a–c. (Ar = C$_6$H$_5$, 4-OHCH$_3$H$_4$, 4-NO$_2$C$_6$H$_4$). Even, IR spectrum of compound 18c showed the ν$_{C=O}$ of hydrazide at ν = 1710 cm$^{-1}$, but we think that derivatives 18a–c are present in equilibrium between the two tautomers: oxadiazoline ring and hydrazone open chain (Scheme 4).

In contrary to similar cases reported by Tominaga [15], the hydrazide 3 when treated with [bis(methylthio)methylene]malononitrile in boiling DMF did not give the expected 5-aminopyrazole-3-carbonitrile 19. The first surprising property of the product of this reaction is the absence of sulfur element. Secondly, no evidences for the presence of an amino (NH$_2$) group in both IR and $^1$H NMR spectra. In addition, $^1$H NMR spectrum clearly shows the loss of both methylthio groups leading to [5-[(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]methyl]-1,3,4-oxadiazol-2(3H)-ylidene]malononitrile (20). The reaction seems to proceed via formation of the expected N$'$-[2,2-dicyano-1-(methylthio)vinyl]-2-[(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]acetohydrazide intermediate, which in turn underwent a thermal intramolecular nucleophilic condensation. To our knowledge, hitherto this is the first description for the use of dimethylthioketene in cyclization of acid hydrazide to oxadiazole (Scheme 4).
Conclusions

Conveniently ester 1, carboxylic acid 2, and hydrazide 3 derivatives of 2-(substituted oxy)-4H-pyrido[1,2-a]pyrimidin-4-one can be used as good synthons to obtain various diazoles, triazoles and fused pyranones of expected biological activity. The ester 1 gives much higher yield than the acid 2 when both are condensed with 1,2-propanediamine whose behavior is inversed towards 1,2-phenylenediamine. Reaction of hydrazide 3 with benzaldehydes furnished tautomeric mixture of hydrazones and predominantly oxadiazolines. Cyclization to oxadiazole with loss of two moles of methanethiol takes place instead of formation of pyrazole when hydrazide 3 is reacted with [bis(methylthio)methylene]malononitrile.

Experimental Section

General

Melting points were determined in open capillary tubes on a digital Gallenkamp MFB-595. IR spectra were taken on a Perkin-Elmer FT-IR 1650, using samples in KBr disks. 1H NMR spectra were recorded on Varian Gemini-200 spectrometer (200 MHz), using DMSO-δ6 as the solvent and TMS as internal reference. Mass spectra were determined on a Shimadzu GC-MS-QP 1000 EX instrument by direct inlet, operating at 70 eV. Elemental microanalyses were performed on an Elmer Elmer CHN-2400 Analyzer. The preparation of ester 1 was previously described [7] and the aldehyde 5 was obtained according to literature [13]. Analytical and spectral data are listed in Tables 1 and 2, respectively.

Ethyl 4-Oxo-4H-furo[2,3-d]pyrido[1,2-a]pyrimidine-2-carboxylate (9)

A mixture of the ester 1 (5 mmol), triethyl orthoformate (6 mmol) and DMF (15 mL) was added and heated in a conical flask at 110–120 °C for 30 min, then the temperature was raised to 140–150 °C gradually over 30 min. After that the mixture was cooled to room temperature and kept in an ice-cold water bath for ca. 2 h. The Yellowish orange crystalline product was filtered and crystallized to give the ester 9.

General Procedure

Equimolar amounts (10 mmol) of the acetate ester 1 and the proper α-hydroxyaldehyde compound namely; salicylaldehyde or 2-hydroxy-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (4), or 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (5), in absolute ethanol (50 mL) containing piperidine (0.2 mL) were heated under reflux for 4–5 h. The crystalline products, which were obtained during the course of the reaction, was filtered while hot and crystallized to give the corresponding pyrones 6, 7 and 8.

2-[(4/5-Methyl-4,5-dihydro-1H-imidazol-2-yl)methoxy]-4H-pyrido-[1,2-a]pyrimidin-4-one (10)

Procedure A.

A mixture of the ester 1 (3 mmol) and 1,2-diaminopropane (3 mmol) was heated without solvent at 180–200 °C for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the imidazolone 10.

Procedure B.

A mixture of the acid 2 (3 mmol) and 1,2-diaminopropane (3 mmol) was heated without solvent at 180–200 °C for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the imidazolone 10.

2-[(1H-Benzimidazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (11)

General Procedure

Equimolar amounts (10 mmol) of the acetate ester 1 and the proper α-hydroxyaldehyde compound namely; salicylaldehyde or 2-hydroxy-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (4), or 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (5), in absolute ethanol (50 mL) containing piperidine (0.2 mL) were heated under reflux for 4–5 h. The crystalline products, which were obtained during the course of the reaction, was filtered while hot and crystallized to give the corresponding pyrones 6, 7 and 8.

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2-[(4/5-Methyl-4,5-dihydro-1H-imidazol-2-yl)methoxy]-4H-pyrido-[1,2-a]pyrimidin-4-one (10)

Procedure A.

A mixture of the ester 1 (3 mmol) and 1,2-diaminopropane (3 mmol) was heated without solvent at 180–200 °C for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the imidazolone 10.

Procedure B.

A mixture of the acid 2 (3 mmol) and 1,2-diaminopropane (3 mmol) was heated without solvent at 180–200 °C for 30 min. Then the mixture was left to cool. The solid product that formed was crystallized to give the imidazolone 10.

2-[(1H-Benzimidazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (11)

General Procedure

Equimolar amounts (10 mmol) of the acetate ester 1 and the proper α-hydroxyaldehyde compound namely; salicylaldehyde or 2-hydroxy-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (4), or 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (5), in absolute ethanol (50 mL) containing piperidine (0.2 mL) were heated under reflux for 4–5 h. The crystalline products, which were obtained during the course of the reaction, was filtered while hot and crystallized to give the corresponding pyrones 6, 7 and 8.

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Equimolar amounts (10 mmol) of the acetate ester 1 and the proper α-hydroxyaldehyde compound namely; salicylaldehyde or 2-hydroxy-4H-pyrido[1,2-a]pyrimidine-3-carboxaldehyde (4), or 4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carboxaldehyde (5), in absolute ethanol (50 mL) containing piperidine (0.2 mL) were heated under reflux for 4–5 h. The crystalline products, which were obtained during the course of the reaction, was filtered while hot and crystallized to give the corresponding pyrones 6, 7 and 8.
Table 1. Analytical Data of the New Compounds.

| Compd. No | Yield % | M.p. °C | Crystaln. Solvent | M. Formula | M. Weight | Microanalysis † Calcd./Found |
|-----------|---------|---------|-------------------|------------|-----------|-----------------------------|
| 2         | 56      | > 300   | EtOH              | C₁₀H₁₆N₂O₄ | 220.19    | C % H % N %  |
| 3         | 80      | 220-2   | EtOH              | C₁₀H₁₀N₂O₃ | 234.22    | 51.28  4.30  23.92 |
| 6         | 68      | 277-8   | DMF               | C₁₁H₁₆N₂O₄ | 306.28    | 66.67  3.29  9.15  |
| 7         | 63      | > 300   | AcOH              | C₁₁H₁₀N₂O₅ | 374.32    | 60.97  2.69  14.97 |
| 8         | 82      | > 300   | AcOH              | C₁₁H₁₀N₂O₅ | 387.35    | 65.12  3.38  10.85 |
| 9         | 81      | 232-4   | Acetone           | C₁₁H₁₀N₂O₄ | 258.24    | 60.47  3.88  10.85 |
| 10        | 55 a    | 188-90  | EtOH              | C₁₂H₁₆N₂O₂ | 258.28    | 60.46  5.46  21.69 |
|           | 7 b     | 188-90  | EtOH              | C₁₂H₁₆N₂O₂ | 258.28    | 60.22  5.27  21.60 |
| 11        | 64      | 242-4   | DMF               | C₁₀H₁₂N₂O₂ | 292.30    | 65.75  4.14  19.17 |
| 12        | 52      | 230-2   | DMF               | C₁₀H₁₁N₂O₃ | 293.28    | 65.53  3.78  14.33 |
| 13        | 78      | 289-91  | DMSO              | C₁₀H₁₄N₄S₂ | 309.35    | 62.12  3.58  13.58 |
| 14        | 65 a    | 205-7   | EtOH              | C₁₁H₁₆N₂O₂ | 290.31    | 45.51  3.47  28.95 |
|           | 72 b    | 205-7   | EtOH              | C₁₁H₁₆N₂O₂ | 290.31    | 45.88  3.24  28.70 |
| 15        | 72 a    | 266-7   | DMF               | C₁₂H₁₅N₃O₃ | 304.33    | 51.31  3.97  18.41 |
|           | 48 b    | 266-7   | DMF               | C₁₂H₁₅N₃O₃ | 304.33    | 51.26  3.98  18.37 |
| 17        | 38      | 196-8   | EtOH              | C₁₁H₁₄N₃S₂ | 322.33    | 63.35  4.38  17.38 |
|           |         |         | EtOH              | C₁₁H₁₄N₃S₂ | 322.33    | 63.50  4.10  17.40 |
| 18 a      | 76      | 230-2   | MeOH              | C₁₂H₁₄N₃O₃ | 338.33    | 60.35  4.17  16.56 |
| 18 b      | 58      | 247-50  | EtOH              | C₁₂H₁₄N₃O₄ | 338.33    | 60.89  3.93  15.89 |
| 18 c      | 55      | 267-8   | EtOH              | C₁₂H₁₃N₃O₅ | 367.32    | 55.59  3.57  19.07 |
| 20        | 75      | 254-6   | DMF               | C₁₂H₁₃N₃O₅ | 308.26    | 54.55  2.62  27.26 |

† Sulfur analysis (S %) for compound 13 calcld. 10.40, Found 10.39, compound 14 calcld. 11.04, Found 10.80, and compound 17 calcld. 10.54, Found 10.40.

‡ and † Yields using procedures A and B, respectively.

for 15 min. Afterwards, the obtained melt was triturated with cold methanol (10 mL) and the solidified product was filtered, washed with methanol and diethyl ether then crystallized to afford the triazole 14.

Procedure B.
To a solution of the acetohydrazide 3 (5 mmol) in ethanol (50 mL, 95 %), fine divided potassium hydroxide (10 mmol) was added followed by drop-wise addition of carbon disulfide (5 mmol) with continuous stirring at 0–5 °C. After complete addition (ca. 20 min), the reaction mixture was stirred for additional 30 min at room temperature, then the obtained yellow precipitate was diluted with water till complete dissolution and hydrazine hydrate (5 mmol) was added. Then the reaction mixture was boiled until the deep greenish brown coloration persisted and left to cool in a crushed-ice bath. The fine crystals so formed were filtered and crystallized to furnish the triazole 14.

2-[(3-Oxo-2,3-dihydro-1H-pyrazol-4-yl)oxy]-4H-pyrido[1,2,3-al]pyrimidin-4-one (15)

Procedure A.
To a solution of the acetohydrazide 3 (5 mmol) in DMF (15 mL), triethyl orthoformate (6 mmol) was added and heated in
Table 2. IR and 1H NMR Spectral Data of the New Compounds.

| Compd. No. | IR (KBr), v/cm⁻¹ | ¹H NMR (DMSO-d₆), δ/ppm |
|------------|------------------|--------------------------|
| 2          | 3508–2667 (b, OH), 1705 (C=O), 1650 (C=O), 1622 (C=N) | 4.54 (s, 2H, OCH₂CO₂H), 5.66 (s, 1H, C3-H), 7.23 (t, 1H, C7-H), 7.48 (d, 1H, C9-H), 7.93 (t, 1H, C8-H), 8.90 (d, 1H, C6-H) |
| 3          | 3333, 3277 (NH₂), 3250, 3197 (NH), 1687 (C=O), 1651 (C=O), 1630 (C=N) | 4.27 (b, 2H, NH₂, exchangeable with D₂O), 4.83 (s, 2H, OCH₂CO₂), 5.74 (s, 1H, C3-H), 7.34 (t, 1H, C7-H), 7.55 (d, 1H, C9-H), 7.97 (t, 1H, C8-H), 8.97 (d, 1H, C6-H), 9.09 (b, 1H, CONH, exchangeable with D₂O) |
| 6          | 1720 (C=O), 1691 (C=O), 1632 (C=N), 1167, 1111 (COC) | 5.46 (s, 1H, C3-H) |
| 7          | 1714 (C=O), 1690-1661 (C=O), 1635 (C=N) | 5.84 (s, 1H, C3'-H), 7.10 (t, 2H, C7'-H + C8-H), 7.34 (d, 2H, C9'-H + C10-H), 7.82 (t, 2H, C8'-H + C9-H), 8.81 (d, 2H, C6'-H + C7-H), 9.57 (s, 1H, C4-H) |
| 8          | 3667, 3299, 3218 (NH), 1688-1645 (C=O), 1630 (C=N), 1145 (C-O-C) | 4.57 (s, 2H, OCH₂), 5.63 (s, 1H, C3-H), 7.31–7.75 (m, 4H, 4H, H₄-atom + C7-H + C9-H), 7.85–8.08 (m, 3H, 2H, H₂-atom + C8-H) |
| 9          | 3289, 3224 (NH), 1660 (C=O), 1630 (C=N) | 1.24 (d, 3H, CH₃), 2.31 (m, 1H, C4'-H), 3.72 (d, 2H, C5'-H), 4.47 (s, 2H, OCH₂), 5.55 (s, 1H, C3-H), 7.35 (t, 1H, C7-H), 7.54 (d, 1H, C9-H), 7.92 (t, 1H, C8-H), 8.96 (d, 1H, C6-H), 9.25–9.45 (b, 1H, NH) |
| 10         | 1301 (C=O), 1640, 1632, 1610 (C=N) | 4.80 (s, 2H, OCH₂), 5.65 (s, 1H, C3-H), 7.19–7.70 (m, 6H, H₄-atom + C7-H + C9-H), 8.05 (d, 1H, C8-H), 8.90 (d, 1H, C6-H) |
| 11         | 1690 (C=O), 1638, 1620, 1608 (C=N) | 4.77 (s, 2H, OCH₂), 5.60 (s, 1H, C3-H), 7.12–7.72 (m, 6H, H₄-atom + C7-H + C9-H), 8.10 (d, 1H, C8-H), 8.84 (d, 1H, C6-H) |
| 12         | 1685 (C=O), 1635, 1618, 1605 (C=N) | 4.13 (s, 2H, OCH₂), 5.06 (s, 1H, C3-H), 6.93 (s, 2H, NH₂), 7.10 (t, 1H, C7-H), 7.33 (d, 1H, C9-H), 7.76 (t, 1H, C8-H), 8.82 (d, 1H, C6-H), 9.93 (s, 1H, NH) |
| 13         | 3440, 3268, 3182 (NH₂), 1645 (C=O), 1632 (C=N) | 5.18 (s, 1H, C3-H), 7.18 (s, 1H, C3-H), 7.57 (t, 1H, C7-H), 7.85 (d, 1H, C9-H), 8.28 (t, 1H, C8-H), 8.98 (d, 1H, C6-H), 9.70 (b, 1H, NH), 10.84 (b, 1H, NHCO) |
| 14         | 3366, 3299, 3218 (NH), 1688-1645 (C=O), 1630 (C=N), 1145 (C-O-C) | 2.61 (d, 3H, CH₃), 3.41 (s, 3H, NCH₃), 5.86 (s, 1H, C3-H), 7.14 (t, 1H, C7-H), 7.37 (d, 1H, C9-H), 8.93 (t, 1H, C8-H), 8.83 (d, 1H, C6-H), 9.67 (s, 1H, NH) |
| 15         | 3250, 3199 (NH), 1688 (C=O), 1651 (C=O), 1635 (C=N) | 4.80 (s, 2H, OCH₂), 5.59 (s, 1H, C5-Hoxadiazoline), 5.70 (s, 1H, C3-H), 7.20–7.48 (m, 7H, H₄-atom + C7-H + C9-H), 8.08 (d, 1H, C8-H), 8.50 (b, 1H, NHoxadiazoline), 8.90 (d, 1H, C9-H) |
| 16         | 3172 (NH), 1692 (C=O), 1625 (C=N), 1120 (C-O-C) | 5.02 (s, 1H, C5-Hoxadiazoline), 5.49 (s, 2H, OCH₂), 5.80 (s, 1H, C3-H), 7.36 (t, 1H, C7-H), 7.56 (d, 1H, C9-H), 7.97–8.04 (m, 3H, 2H, H₂-atom + C8-H), 8.13 (s, 1H, NHoxadiazoline), 8.29 (d, 2H, H₂-atom), 8.98 (d, 1H, C9-H), 11.89 (s, 1H, OH) |
| 17         | 3186 (NH), 2630 (br, OH), 1697 (C=O), 1632 (C=N), 1126 (C-O-C) | 4.82 (s, 2H, OCH₂), 5.66 (s, 1H, C5-Hoxadiazoline), 5.85 (s, 1H, C3-H), 7.22–7.60 (m, 4H, H₄-atom + C7-H + C9-H), 7.90–8.20 (m, 3H, H₄-atom + C8-H), 8.80 (b, 1H, NHoxadiazoline), 8.92 (d, 1H, C9-H) |
| 18         | 3123 (NH), 1710 (C=O), 1677 (C=O), 1631 (C=N), 3216, 3113 (NH), 2213 (C=N), 1691 (C=O), 1628 (C=N), 1146 (C-O-C) | 4.93 (s, 2H, OCH₂), 5.76 (s, 1H, C3-H), 7.39 (t, 1H, C7-H), 7.56 (d, 1H, C9-H), 7.99 (t, 1H, C8-H), 8.94 (d, 1H, C6-H), 10.25 (s, 1H, NHoxadiazole, exchangeable with D₂O) |
a conical flask at 110-120 °C for 30 min, then the temperature was raised to 140–150 °C gradually over 30 min. After that the mixture was cooled to room temperature and kept in an ice-cold water bath for ca. 2 h. The Yellowish orange crystalline product was filtered and crystallized to give the compound 15.

Procedure B.
A mixture of acetoxydrazide 3 (5 mmol) and triethyl orthoformate (15 mmol) was heated under reflux for 2 h. After that the mixture was cooled to room temperature and triturated with cold methanol (10 mL). The solid so formed was filtered off and crystallized to give the compound 15.

2-[(2-Methyl-5-(methylthio)-3-oxo-2,3-dihydro-1H-pyrazol-4-yl)oxy]-4H-pyrido[1,2-a]pyrimidin-4-one (17)

To a solution of the acetoxydrazide 3 (5 mmol), in absolute ethanol (50 mL), sodium ethoxide (15 mmol) was added, followed by drop-wise addition of carbon disulfide (5 mmol) with continuous stirring in and ice-cold water bath at 0-5 °C. After complete addition, the mixture was stirred at room temperature for 30 min and methyl iodide (20 mmol) was dropped over a period of ca. 20 min, then the reactor was fitted with reflux condenser and heated at boiling for 1h. After cooling, the crystalline deposits were collected by filtration, washed with cold ethanol and crystallized to afford the pyrazole 17.

2-[(5-Phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (18a), 2-[(5-(4-Hydroxyphenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (18b), and 2-[(5-(4-Nitrophenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-4H-pyrido[1,2-a]pyrimidin-4-one (18c)

General Procedure
A mixture of the acetoxydrazide 12 (3 mmol) and benzaldehyde or 4-hydroxybenzaldehyde, or 4-nitrobenzaldehyde (3 mmol), in absolute ethanol (20 mL), was treated with piperidine (0.1 mL). The clear solution was then heated under reflux for 2 h. The solid precipitate so formed during the course of the reaction was collected by filtration and crystallized to give the 1,3,4-oxadiazolines 18a-c.

[5-[(4-Oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)oxy]methyl]-1,3,4-oxadiazol-2(3H)-yldene]-malononitrile (20)

A mixture of the acetoxydrazide 3 (15 mmol) and [bis(methylthio)methylene]-malononitrile (6 mmol), in DMF (20 mL) was heated under reflux till evolution of methanethiol ceased (ca. 1h). Then, the reaction solution was left to cool at room temperature and the crystalline precipitate so formed was filtered and crystallized to give the 1,3,4-oxadiazole 20.

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